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09/288,950 9 April 1999 (09.04.1999) US
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(71) Applicant *(for all designated States except US)*: **CORIXA CORPORATION** [US/US]; Suite 200, 1124 Columbia Street, Seattle, WA 98104 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **REED, Steven, G.** [US/US]; 2843 - 122nd Place NE, Bellevue, WA 98005 (US). **XU, Jiangchun** [US/US]; 15805 SE 43rd Place, Bellevue, WA 98006 (US). **DILLON, Davin, C.** [US/US]; 21607 NE 24th Street, Redmond, WA 98053 (US).

(74) Agents: **POTTER, Jane, E.R.**; Seed Intellectual Property Law Group PLLC, Suite 6300, 701 Fifth Avenue, Seattle, WA 98104-7092 et al. (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/61756 A3

(54) Title: COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

(57) Abstract: Compounds and methods for the treatment and diagnosis of breast cancer are provided. The inventive compounds include polypeptides containing at least a portion of a breast tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of breast cancer comprising such polypeptides, or polynucleotides encoding such polypeptides, are also provided, together with polynucleotides for preparing the inventive polypeptides.

INTERNATIONAL SEARCH REPORT

Intern. ,nal Application No
PCT/US 00/09688

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C12N15/62 C07K14/47 C07K16/18 A61K35/12 A61K38/17 A61K39/00 A61P35/00 G01N33/53 C12Q1/68 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K A61P G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 679 716 A (MATSUBARA KENICHI ;OKUBO KOUSAKU (JP)) 2 November 1995 (1995-11-02) HUMGS01423/SeqIdNo.1275: 82.6% identity in 149 bp overlap with SeqIdNo.3 ---	1,3-12, 18-35, 37-60
A	DATABASE EMEST [Online] E.B.I., Hinxton, U.K.; Accession Number: AA749298, 20 January 1998 (1998-01-20) NCI-CGAP: "Homo sapiens cDNA clone IMAGE:1271152 3', mRNA sequence" XP002146686 abstract ---	
A	WO 95 19783 A (CELIS ESTEBAN ;GREY HOWARD M (US); CYTEL CORP (US); KUBO RALPH T () 27 July 1995 (1995-07-27) --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 September 2000	04. 12. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lonnoy, O

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/09688

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCHLOM J ET AL: "STRATEGIES FOR THE DEVELOPMENT OF RECOMBINANT VACCINES FOR THE IMMUNOTHERAPY OF BREAST CANCER" BREAST CANCER RESEARCH AND TREATMENT, US, NIJHOFF, BOSTON, vol. 38, no. 1, 1996, pages 27-39, XP000578043 ISSN: 0167-6806 ---	
A	WO 97 02280 A (HUMAN GENOME SCIENCES INC) 23 January 1997 (1997-01-23) ---	
P,X	WO 99 33869 A (CORIXA CORP) 8 July 1999 (1999-07-08) SeqIdNo.3: 100.0% identity in 421 bp overlap with SeqIdNo.3 -----	1,3-12, 18-35, 37-60

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/09688

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 48-53 and 56-58 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1,3-12,18-35,37-60 (all partially)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1,3-12,18-35,37-60 (all partially)
An isolated polypeptide comprising an immunogenic portion of a breast protein or a variant thereof, encoded by a polynucleotide comprising the sequence of SeqIdNo.3; said polynucleotide; a vector and a host comprising the polynucleotide; its use for the production of the polypeptide or antibodies reactive with the polypeptide; its use for the manufacture of a pharmaceutical composition or a vaccine; its use for the detection of breast proteins or nucleic acids.

Inventions 2 to 104: Claims 1-60 (all partially, as applicable)
Idem as invention 1, wherein

Inventions 2-38 relate to the individual nucleic acids and their corresponding polypeptides in the order as they occur in claim 1, where invention 2 is limited to SeqIdNo.10, invention 3 to SeqIdNo.17, invention 4 to SeqIdNo.24, inventions 5-12 respectively to SeqIdNos.45-52, inventions 13-25 respectively to SeqIdNos.55-67, invention 26 to SeqIdNo.72, invention 27 to SeqIdNo.73, invention 28-33 respectively to SeqIdNos.89-94, invention 34 to SeqIdNo.95 and SeqIdNo.98, invention 35 to SeqIdNo.96 and 99, invention 36 to SeqIdNo.97, invention 37 to SeqIdNo.102, and invention 38 to SeqIdNo.107;

Inventions 39-103 relate to the individual nucleic acids and their corresponding polypeptides in the order as they occur in claim 13, where invention 39 is limited to SeqIdNo.1, invention 40 to SeqIdNo.2, inventions 41-46 to SeqIdNos.4-9, inventions 47-52 to SeqIdNo.11-16, inventions 53-58 to SeqIdNo.18-23, inventions 59-78 to SeqIdNo.25-44, invention 79 to SeqIdNo.53, invention 80 to SeqIdNo.54, inventions 81-84 to SeqIdNo.68-71, inventions 85-99 to SeqIdNo.74-88, and inventions 100-103 to SeqIdNo.103-106; and

Invention 104 relates to the individual nucleic acid of SeqIdNo.100 and the corresponding polypeptide of SeqIdNo.101.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern...onal Application No
PCT/US 00/09688

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0679716 A	02-11-1995	AU 8116494 A	13-06-1995
		CA 2153480 A	01-06-1995
		WO 9514772 A	01-06-1995
WO 9519783 A	27-07-1995	US 5662907 A	02-09-1997
		AU 1834095 A	08-08-1995
		AU 4111999 A	23-09-1999
		CA 2181920 A	27-07-1995
		EP 0749315 A	27-12-1996
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		AU 3092995 A	05-02-1997
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		EP 1042360 A	11-10-2000
		ZA 9811800 A	23-06-1999

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Published

Without international search report and to be republished upon receipt of that report.

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(57) Abstract

Compounds and methods for the treatment and diagnosis of breast cancer are provided. The inventive compounds include polypeptides containing at least a portion of a breast tumor protein. Vaccines and pharmaceutical compositions for immunotherapy of breast cancer comprising such polypeptides, or polynucleotides encoding such polypeptides, are also provided, together with polynucleotides for preparing the inventive polypeptides.

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MX	Mexico
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NL	Netherlands
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TT	Trinidad and Tobago
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UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam
YU	Yugoslavia
ZW	Zimbabwe

COMPOUNDS FOR IMMUNOTHERAPY AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment and diagnosis of breast cancer. The invention is more particularly related to polypeptides comprising at least a portion of a protein that is preferentially expressed in breast tumor tissue and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for treatment of breast cancer. Additionally such polypeptides and polynucleotides may be used in the immunodiagnosis of breast cancer.

BACKGROUND OF THE INVENTION

Breast cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and treatment of the disease, breast cancer remains the second leading cause of cancer-related deaths in women, affecting more than 180,000 women in the United States each year. For women in North America, the life-time odds of getting breast cancer are now one in eight.

No vaccine or other universally successful method for the prevention or treatment of breast cancer is currently available. Management of the disease currently relies on a combination of early diagnosis (through routine breast screening procedures) and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular breast cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. *See*, *e.g.*, Porter-Jordan and Lippman, *Breast Cancer* *8*:73-100 (1994). However, the use of established markers often leads to a result that is difficult to interpret, and the high

mortality observed in breast cancer patients indicates that improvements are needed in the treatment, diagnosis and prevention of the disease.

Accordingly, there is a need in the art for improved methods for therapy and diagnosis of breast cancer. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

The present invention provides compounds and methods for immunotherapy of breast cancer. In one aspect, isolated polypeptides are provided comprising at least an immunogenic portion of a breast tumor protein or a variant of said protein that differs only in conservative substitutions and/or modifications, wherein the breast tumor protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-97, 102 and 107, (b) complements of said nucleotide sequences and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions. In specific embodiments, the isolated polypeptides of the present invention comprise an amino acid sequence of SEQ ID NO: 98, 99 or 101.

In related aspects, isolated polynucleotides encoding the above polypeptides are provided. In specific embodiments, such polynucleotides comprise sequences provided in SEQ ID NOS: 3, 10, 17, 24, 45-52 and 55-67, 72, 73, 89-97, 102 and 107. The present invention further provides expression vectors comprising the above polynucleotides and host cells transformed or transfected with such expression vectors. In preferred embodiments, the host cells are selected from the group consisting of *E. coli*, yeast and mammalian cells.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known breast antigen.

The present invention also provides pharmaceutical compositions comprising at least one of the above polypeptides, or a polynucleotide encoding such a polypeptide, and a physiologically acceptable carrier, together with vaccines

comprising at least one or more such polypeptide or polynucleotide in combination with a non-specific immune response enhancer. Pharmaceutical compositions and vaccines comprising one or more of the above fusion proteins are also provided.

In related aspects, pharmaceutical compositions for the treatment of breast cancer comprising at least one polypeptide and a physiologically acceptable carrier are provided, wherein the polypeptide comprises an immunogenic portion of a breast tumor protein or a variant thereof, the breast tumor protein being encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106, (b) complements of said nucleotide sequences, and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions. The invention also provides vaccines for the treatment of breast cancer comprising such polypeptides in combination with a non-specific immune response enhancer, together with pharmaceutical compositions and vaccines comprising at least one polynucleotide comprising a sequence provided in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106.

In yet another aspect, methods are provided for inhibiting the development of breast cancer in a patient, comprising administering an effective amount of at least one of the above pharmaceutical compositions and/or vaccines.

The present invention also provides methods for immunodiagnosis of breast cancer, together with kits for use in such methods. In one specific aspect of the present invention, methods are provided for detecting breast cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the above polypeptides; and (b) detecting in the sample a protein or polypeptide that binds to the binding agent. In preferred embodiments, the binding agent is an antibody, most preferably a monoclonal antibody.

In related aspects, methods are provided for monitoring the progression of breast cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one

of the above polypeptides; (b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent; (c) repeating steps (a) and (b); and comparing the amounts of polypeptide detected in steps (b) and (c).

Within related aspects, the present invention provides antibodies, preferably monoclonal antibodies, that bind to the inventive polypeptides, as well as diagnostic kits comprising such antibodies, and methods of using such antibodies to inhibit the development of breast cancer.

The present invention further provides methods for detecting breast cancer comprising: (a) obtaining a biological sample from a patient; (b) contacting the sample with a first and a second oligonucleotide primer in a polymerase chain reaction, at least one of the oligonucleotide primers being specific for a polynucleotide that encodes one of the above polypeptides; and (c) detecting in the sample a DNA sequence that amplifies in the presence of the first and second oligonucleotide primers. In a preferred embodiment, at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97, 100 and 102-107.

In a further aspect, the present invention provides a method for detecting breast cancer in a patient comprising: (a) obtaining a biological sample from the patient; (b) contacting the sample with an oligonucleotide probe specific for a polynucleotide that encodes one of the above polypeptides; and (c) detecting in the sample a polynucleotide sequence that hybridizes to the oligonucleotide probe. Preferably, the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97, 100 and 102-107.

In related aspects, diagnostic kits comprising the above oligonucleotide probes or primers are provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein

are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figs. 1A and B show the specific lytic activity of a first and a second B511S-specific CTL clone, respectively, measured on autologous LCL transduced with B511s (filled squares) or HLA-A3 (open squares).

SEQ ID NO: 1 is the determined 3'cDNA sequence of 1T-5120
SEQ ID NO: 2 is the determined 3'cDNA sequence of 1T-5122
SEQ ID NO: 3 is the determined 3'cDNA sequence of 1T-5123
SEQ ID NO: 4 is the determined 3'cDNA sequence of 1T-5125
SEQ ID NO: 5 is the determined 3'cDNA sequence of 1T-5126
SEQ ID NO: 6 is the determined 3'cDNA sequence of 1T-5127
SEQ ID NO: 7 is the determined 3'cDNA sequence of 1T-5129
SEQ ID NO: 8 is the determined 3'cDNA sequence of 1T-5130
SEQ ID NO: 9 is the determined 3'cDNA sequence of 1T-5133
SEQ ID NO: 10 is the determined 3'cDNA sequence of 1T-5136
SEQ ID NO: 11 is the determined 3'cDNA sequence of 1T-5137
SEQ ID NO: 12 is the determined 3'cDNA sequence of 1T-5139
SEQ ID NO: 13 is the determined 3'cDNA sequence of 1T-5142
SEQ ID NO: 14 is the determined 3'cDNA sequence of 1T-5143
SEQ ID NO: 15 is the determined 5'cDNA sequence of 1T-5120
SEQ ID NO: 16 is the determined 5'cDNA sequence of 1T-5122
SEQ ID NO: 17 is the determined 5'cDNA sequence of 1T-5123
SEQ ID NO: 18 is the determined 5'cDNA sequence of 1T-5125
SEQ ID NO: 19 is the determined 5'cDNA sequence of 1T-5126
SEQ ID NO: 20 is the determined 5'cDNA sequence of 1T-5127
SEQ ID NO: 21 is the determined 5'cDNA sequence of 1T-5129
SEQ ID NO: 22 is the determined 5'cDNA sequence of 1T-5130

SEQ ID NO: 23 is the determined 5'cDNA sequence of 1T-5133

SEQ ID NO: 24 is the determined 5'cDNA sequence of 1T-5136

SEQ ID NO: 25 is the determined 5'cDNA sequence of 1T-5137

SEQ ID NO: 26 is the determined 5'cDNA sequence of 1T-5139

SEQ ID NO: 27 is the determined 5'cDNA sequence of 1T-5142

SEQ ID NO: 28 is the determined 5'cDNA sequence of 1T-5143

SEQ ID NO: 29 is the determined 5'cDNA sequence of 1D-4315

SEQ ID NO: 30 is the determined 5'cDNA sequence of 1D-4311

SEQ ID NO: 31 is the determined 5'cDNA sequence of 1E-4440

SEQ ID NO: 32 is the determined 5'cDNA sequence of 1E-4443

SEQ ID NO: 33 is the determined 5'cDNA sequence of 1D-4321

SEQ ID NO: 34 is the determined 5'cDNA sequence of 1D-4310

SEQ ID NO: 35 is the determined 5'cDNA sequence of 1D-4320

SEQ ID NO: 36 is the determined 5'cDNA sequence of 1E-4448

SEQ ID NO: 37 is the determined 5'cDNA sequence of 1S-5105

SEQ ID NO: 38 is the determined 5'cDNA sequence of 1S-5110

SEQ ID NO: 39 is the determined 5'cDNA sequence of 1S-5111

SEQ ID NO: 40 is the determined 5'cDNA sequence of 1S-5116

SEQ ID NO: 41 is the determined 5'cDNA sequence of 1S-5114

SEQ ID NO: 42 is the determined 5'cDNA sequence of 1S-5115

SEQ ID NO: 43 is the determined 5'cDNA sequence of 1S-5118

SEQ ID NO: 44 is the determined 5'cDNA sequence of 1T-5134

SEQ ID NO: 45 is the determined 5'cDNA sequence of 1E-4441

SEQ ID NO: 46 is the determined 5'cDNA sequence of 1E-4444

SEQ ID NO: 47 is the determined 5'cDNA sequence of 1E-4322

SEQ ID NO: 48 is the determined 5'cDNA sequence of 1S-5103

SEQ ID NO: 49 is the determined 5'cDNA sequence of 1S-5107

SEQ ID NO: 50 is the determined 5'cDNA sequence of 1S-5113

SEQ ID NO: 51 is the determined 5'cDNA sequence of 1S-5117

SEQ ID NO: 52 is the determined 5'cDNA sequence of 1S-5112

SEQ ID NO: 53 is the determined cDNA sequence of 1013E11

SEQ ID NO: 54 is the determined cDNA sequence of 1013H10

SEQ ID NO: 55 is the determined cDNA sequence of 1017C2

SEQ ID NO: 56 is the determined cDNA sequence of 1016F8

SEQ ID NO: 57 is the determined cDNA sequence of 1015F5

SEQ ID NO: 58 is the determined cDNA sequence of 1017A11

SEQ ID NO: 59 is the determined cDNA sequence of 1013A11

SEQ ID NO: 60 is the determined cDNA sequence of 1016D8

SEQ ID NO: 61 is the determined cDNA sequence of 1016D12

SEQ ID NO: 62 is the determined cDNA sequence of 1015E8

SEQ ID NO: 63 is the determined cDNA sequence of 1015D11

SEQ ID NO: 64 is the determined cDNA sequence of 1012H8

SEQ ID NO: 65 is the determined cDNA sequence of 1013C8

SEQ ID NO: 66 is the determined cDNA sequence of 1014B3

SEQ ID NO: 67 is the determined cDNA sequence of 1015B2

SEQ ID NO: 68-71 are the determined cDNA sequences of previously identified antigens

SEQ ID NO: 72 is the determined cDNA sequence of JJ9434

SEQ ID NO: 73 is the determined cDNA sequence of B535S

SEQ ID NO: 74-88 are the determined cDNA sequence of previously identified antigens

SEQ ID NO: 89 is the determined cDNA sequence of B534S

SEQ ID NO: 90 is the determined cDNA sequence of B538S

SEQ ID NO: 91 is the determined cDNA sequence of B542S

SEQ ID NO: 92 is the determined cDNA sequence of B543S

SEQ ID NO: 93 is the determined cDNA sequence of P501S

SEQ ID NO: 94 is the determined cDNA sequence of B541S

SEQ ID NO: 95 is an extended cDNA sequence for 1016F8 (also referred to as B511S)

SEQ ID NO: 96 is an extended cDNA sequence for 1016D12 (also referred to as

B532S)

SEQ ID NO: 97 is an extended cDNA sequence for 1012H8 (also referred to as B533S)

SEQ ID NO: 98 is the predicted amino acid sequence for B511S

SEQ ID NO: 99 is the predicted amino acid sequence for B532S

SEQ ID NO: 100 is the determined full-length cDNA sequence for P501S

SEQ ID NO: 101 is the predicted amino acid sequence for P501S

SEQ ID NO: 102 is the determined cDNA sequence of clone #19605, also referred to as 1017C2, showing no significant homology to any known gene

SEQ ID NO: 103 is the determined 3' end cDNA sequence for clone #19599, showing homology to the Tumor Expression Enhanced gene

SEQ ID NO: 104 is the determined 5' end cDNA sequence for clone #19599, showing homology to the Tumor Expression Enhanced gene

SEQ ID NO: 105 is the determined cDNA sequence for clone #19607, showing homology to Stromelysin-3

SEQ ID NO: 106 is the determined cDNA sequence for clone #19601, showing homology to Collagen

SEQ ID NO: 107 is the determined cDNA sequence of clone #19606, also referred to as B546S, showing no signigicant homology to any known gene

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the immunotherapy and diagnosis of breast cancer. The inventive compositions are generally isolated polypeptides that comprise at least a portion of a breast tumor protein. Also included within the present invention are molecules (such as an antibody or fragment thereof) that bind to the inventive polypeptides. Such molecules are referred to herein as "binding agents."

In particular, the subject invention discloses isolated polypeptides comprising at least a portion of a human breast tumor protein, or a variant thereof, wherein the breast tumor protein includes an amino acid sequence encoded by a

polynucleotide molecule including a sequence selected from the group consisting of: nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, the complements of said nucleotide sequences, and variants thereof. In certain specific embodiments, the inventive polypeptides comprise an amino acid sequence selected from the group consisting of sequences provided in SEQ ID NO: 98, 99 and 101, and variants thereof. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full length proteins, wherein the amino acid residues are linked by covalent peptide bonds. Thus, a polypeptide comprising a portion of one of the above breast proteins may consist entirely of the portion, or the portion may be present within a larger polypeptide that contains additional sequences. The additional sequences may be derived from the native protein or may be heterologous, and such sequences may be immunoreactive and/or antigenic.

As used herein, an "immunogenic portion" of a human breast tumor protein is a portion that is capable of eliciting an immune response in a patient inflicted with breast cancer and as such binds to antibodies present within sera from a breast cancer patient. Such immunogenic portions generally comprise at least about 5 amino acid residues, more preferably at least about 10, and most preferably at least about 20 amino acid residues. Immunogenic portions of the proteins described herein may be identified in antibody binding assays. Such assays may generally be performed using any of a variety of means known to those of ordinary skill in the art, as described, for example, in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988. For example, a polypeptide may be immobilized on a solid support (as described below) and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A. Alternatively, a polypeptide may be used to generate monoclonal and polyclonal antibodies for use in detection of the polypeptide in blood or other fluids of breast cancer patients. Methods for preparing and identifying immunogenic portions of antigens of known sequence are well known

in the art and include those summarized in Paul, *Fundamental Immunology*, 3rd ed., Raven Press, 1993, pp. 243-247.

The term "polynucleotide(s)," as used herein, means a single or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases and includes DNA and corresponding RNA molecules, including HnRNA and mRNA molecules, both sense and anti-sense strands, and comprehends cDNA, genomic DNA and recombinant DNA, as well as wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and corresponds to a DNA molecule in a generally one-to-one manner. An mRNA molecule corresponds to an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide may consist of an entire gene, or any portion thereof. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all such operable anti-sense fragments.

The compositions and methods of the present invention also encompass variants of the above polypeptides and polynucleotides. A polypeptide "variant," as used herein, is a polypeptide that differs from the recited polypeptide only in conservative substitutions and/or modifications, such that the therapeutic, antigenic and/or immunogenic properties of the polypeptide are retained. In a preferred embodiment, variant polypeptides differ from an identified sequence by substitution, deletion or addition of five amino acids or fewer. Such variants may generally be identified by modifying one of the above polypeptide sequences, and evaluating the antigenic properties of the modified polypeptide using, for example, the representative procedures described herein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described below) to the identified polypeptides.

As used herein, a "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. In general, the

following groups of amino acids represent conservative changes: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his.

Variants may also, or alternatively, contain other modifications, including the deletion or addition of amino acids that have minimal influence on the antigenic properties, secondary structure and hydropathic nature of the polypeptide. For example, a polypeptide may be conjugated to a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

A nucleotide "variant" is a sequence that differs from the recited nucleotide sequence in having one or more nucleotide deletions, substitutions or additions. Such modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA, 2*:183, 1983). Nucleotide variants may be naturally occurring allelic variants, or non-naturally occurring variants. Variant nucleotide sequences preferably exhibit at least about 70%, more preferably at least about 80% and most preferably at least about 90% identity (determined as described below) to the recited sequence.

The antigens provided by the present invention include variants that are encoded by DNA sequences which are substantially homologous to one or more of the DNA sequences specifically recited herein. "Substantial homology," as used herein, refers to DNA sequences that are capable of hybridizing under moderately stringent conditions. Suitable moderately stringent conditions include prewashing in a solution of 5X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65° C, 5X SSC, overnight or, in the event of cross-species homology, at 45°C with 0.5X SSC; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. Such hybridizing DNA sequences are also within

the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode an immunogenic polypeptide that is encoded by a hybridizing DNA sequence.

Two nucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, more preferably 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Resarch Foundaiton, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) Fast and sensitive multiple sequence alignments on a microcomputer *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) Optimal alignments in linear space *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) The neighbor joining method. A new method for reconstructing phylogenetic trees *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Rapid similarity searches of nucleic acid and protein data banks *Proc. Natl. Acad., Sci. USA 80*:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Also included in the scope of the present invention are alleles of the genes encoding the nucleotide sequences recited herein. As used herein, an "allele" or "allellic sequence" is an alternative form of the gene which may result from at least one mutation in the nucleic acid sequence. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. Any given gene may have none, one, or many allelic forms. Common mutational changes which give rise to alleles are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone or in combination with the others, one or more times in a given sequence.

For breast tumor polypeptides with immunoreactive properties, variants may alternatively be identified by modifying the amino acid sequence of one of the above polypeptides, and evaluating the immunoreactivity of the modified polypeptide. For breast tumor polypeptides useful for the generation of diagnostic binding agents, a variant may be identified by evaluating a modified polypeptide for the ability to generate antibodies that detect the presence or absence of breast cancer. Such modified sequences may be prepared and tested using, for example, the representative procedures described herein.

The breast tumor proteins of the present invention, and polynucleotide molecules encoding such proteins, may be isolated from breast tumor tissue using any

of a variety of methods well known in the art. Polynucleotide sequences corresponding to a gene (or a portion thereof) encoding one of the inventive breast tumor proteins may be isolated from a breast tumor cDNA library using a subtraction technique as described in detail below. Examples of such DNA sequences are provided in SEQ ID NOS: 1- 97, 100 and 102-107. Partial polynucleotide sequences thus obtained may be used to design oligonucleotide primers for the amplification of full-length polynucleotide sequences in a polymerase chain reaction (PCR), using techniques well known in the art (see, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol., 51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989). Once a polynucleotide sequence encoding a polypeptide is obtained, any of the above modifications may be readily introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis as taught, for example, by Adelman et al. (*DNA, 2*:183, 1983).

The breast tumor polypeptides disclosed herein may also be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain (see, for example, Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963). Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Alternatively, any of the above polypeptides may be produced recombinantly by inserting a polynucleotide sequence that encodes the polypeptide into an expression vector and expressing the protein in an appropriate host. Any of a variety of expression vectors known to those of ordinary skill in the art may be employed to express recombinant polypeptides of this invention. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an

expression vector containing a polynucleotide molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line, such as CHO cells. The polynucleotide sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In general, regardless of the method of preparation, the polypeptides disclosed herein are prepared in an isolated, substantially pure form (*i.e.*, the polypeptides are homogenous as determined by amino acid composition and primary sequence analysis). Preferably, the polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. In certain preferred embodiments, described in more detail below, the substantially pure polypeptides are incorporated into pharmaceutical compositions or vaccines for use in one or more of the methods disclosed herein.

In a related aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, a polypeptide of the present invention and a known breast tumor antigen, together with variants of such fusion proteins.

A polynucleotide sequence encoding a fusion protein of the present invention is constructed using known recombinant DNA techniques to assemble separate polynucleotide sequences encoding the first and second polypeptides into an appropriate expression vector. The 3' end of a polynucleotide sequence encoding the first polypeptide is ligated, with or without a peptide linker, to the 5' end of a polynucleotide sequence encoding the second polypeptide so that the reading frames of the sequences are in phase to permit mRNA translation of the two DNA sequences into a single fusion protein that retains the biological activity of both the first and the second polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptides by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is

incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may be from 1 to about 50 amino acids in length. Peptide sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated polynucleotide sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of polynucleotides are located only 5' to the polynucleotide sequence encoding the first polypeptide. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the polynucleotide sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. *New Engl. J. Med., 336*:86-91 (1997)).

Polypeptides of the present invention that comprise an immunogenic portion of a breast tumor protein may generally be used for immunotherapy of breast cancer, wherein the polypeptide stimulates the patient's own immune response to breast tumor cells. In further aspects, the present invention provides methods for using one or more of the immunoreactive polypeptides encoded by a polynucleotide

molecule having a sequence provided in SEQ ID NOS: 1- 97, 100 and 102-107 (or fusion proteins comprising one or more such polypeptides and/or polynucleotides encoding such polypeptides) for immunotherapy of breast cancer in a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may be afflicted with a disease, or may be free of detectable disease. Accordingly, the above immunoreactive polypeptides (or fusion proteins or polynucleotide molecules encoding such polypeptides) may be used to treat breast cancer or to inhibit the development of breast cancer. In a preferred embodiment, the polypeptides are administered either prior to or following surgical removal of primary tumors and/or treatment by administration of radiotherapy and conventional chemotherapeutic drugs.

In these aspects, the polypeptide or fusion protein is generally present within a pharmaceutical composition and/or a vaccine. Pharmaceutical compositions may comprise one or more polypeptides, each of which may contain one or more of the above sequences (or variants thereof), and a physiologically acceptable carrier. The vaccines may comprise one or more of such polypeptides and a non-specific immune response enhancer, wherein the non-specific immune response enhancer is capable of eliciting or enhancing an immune response to an exogenous antigen. Examples of non-specific-immune response enhancers include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the polypeptide is incorporated). Pharmaceutical compositions and vaccines may also contain other epitopes of breast tumor antigens, either incorporated into a combination polypeptide (*i.e.*, a single polypeptide that contains multiple epitopes) or present within a separate polypeptide.

Alternatively, a pharmaceutical composition or vaccine may contain polynucleotides encoding one or more of the above polypeptides, such that the polypeptide is generated *in situ*. In such pharmaceutical compositions and vaccines, the polynucleotide may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Appropriate nucleic acid expression systems

contain the necessary polynucleotide sequences for expression in the patient (such as a suitable promoter). Bacterial delivery systems involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an epitope of a breast tumor cell antigen on its cell surface. In a preferred embodiment, the polynucleotide molecules may be introduced using a viral expression system (*e.g.*, vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., *PNAS 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *PNAS 91*:215-219, 1994; Kass-Eisler et al., *PNAS 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993. Techniques for incorporating polynucleotides into such expression systems are well known to those of ordinary skill in the art.

The polynucleotides may also be "naked," as described, for example, in published PCT application WO 90/11092, and Ulmer et al., *Science 259*:1745-1749, 1993, reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked polynucleotides may be increased by coating the polynucleotides onto biodegradable beads, which are efficiently transported into the cells.

Routes and frequency of administration, as well as dosage, will vary from individual to individual and may parallel those currently being used in immunotherapy of other diseases. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Between 1 and 10 doses may be administered over a 3-24 week period. Preferably, 4 doses are administered, at an interval of 3 months, and booster administrations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of polypeptide or polynucleotide that is

effective to raise an immune response (cellular and/or humoral) against breast tumor cells in a treated patient. A suitable immune response is at least 10-50% above the basal (*i.e.*, untreated) level. In general, the amount of polypeptide present in a dose (or produced *in situ* by the polynucleotide in a dose) ranges from about 1 pg to about 100 mg per kg of host, typically from about 10 pg to about 1 mg, and preferably from about 100 pg to about 1 µg. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.01 mL to about 5 mL.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a lipid, a wax and/or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and/or magnesium carbonate, may be employed. Biodegradable microspheres (*e.g.*, polylactic glycolide) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a nonspecific stimulator of immune response, such as lipid A, *Bordella pertussis* or *Mycobacterium tuberculosis*. Such adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI) and Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ).

Polypeptides disclosed herein may also be employed in adoptive immunotherapy for the treatment of cancer. Adoptive immunotherapy may be broadly classified into either active or passive immunotherapy. In active immunotherapy, treatment relies on the *in vivo* stimulation of the endogenous host

immune system to react against tumors with the administration of immune response-modifying agents (for example, tumor vaccines, bacterial adjuvants, and/or cytokines).

In passive immunotherapy, treatment involves the delivery of biologic reagents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T lymphocytes (for example, CD8+ cytotoxic T-lymphocyte, CD4+ T-helper, gamma/delta T lymphocytes, tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells, lymphokine-activated killer cells), B cells, or antigen presenting cells (such as dendritic cells and macrophages) expressing the disclosed antigens. The polypeptides disclosed herein may also be used to generate antibodies or anti-idiotypic antibodies (as in U.S. Patent No. 4,918,164), for passive immunotherapy.

The predominant method of procuring adequate numbers of T-cells for adoptive immunotherapy is to grow immune T-cells *in vitro*. Culture conditions for expanding single antigen-specific T-cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. These *in vitro* culture conditions typically utilize intermittent stimulation with antigen, often in the presence of cytokines, such as IL-2, and non-dividing feeder cells. As noted above, the immunoreactive polypeptides described herein may be used to rapidly expand antigen-specific T cell cultures in order to generate sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B-cells, may be pulsed with immunoreactive polypeptides or polynucleotide sequence(s) may be introduced into antigen presenting cells, using standard techniques well known in the art. For example, antigen presenting cells may be transfected or transduced with a polynucleotide sequence, wherein said sequence contains a promoter region appropriate for inducing expression, and can be expressed as part of a recombinant virus or other expression system. Several viral vectors may be used to transduce an antigen presenting cell, including pox virus, vaccinia virus, and adenovirus. Antigen presenting cells may be

transfected with polynucleotide sequences disclosed herein by a variety of means, including gene-gun technology, lipid-mediated delivery, electroporation, osmotic shock, and particulate delivery mechanisms, resulting in efficient and acceptable expression levels as determined by one of ordinary skill in the art. For cultured T-cells to be effective in therapy, the cultured T-cells must be able to grow and distribute widely and to survive long term *in vivo*. Studies have demonstrated that cultured T-cells can be induced to grow *in vivo* and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever, M., et al, "Therapy With Cultured T Cells: Principles Revisited," *Immunological Reviews, 157*:177, 1997).

The polypeptides disclosed herein may also be employed to generate and/or isolate tumor-reactive T-cells, which can then be administered to the patient. In one technique, antigen-specific T-cell lines may be generated by *in vivo* immunization with short peptides corresponding to immunogenic portions of the disclosed polypeptides. The resulting antigen specific CD8+ CTL clones may be isolated from the patient, expanded using standard tissue culture techniques, and returned to the patient.

Alternatively, peptides corresponding to immunogenic portions of the polypeptides may be employed to generate tumor reactive T cell subsets by selective *in vitro* stimulation and expansion of autologous T cells to provide antigen-specific T cells which may be subsequently transferred to the patient as described, for example, by Chang et al. *(Crit. Rev. Oncol. Hematol., 22*(3), 213, 1996). Cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system. The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

In other embodiments, T-cell and/or antibody receptors specific for the polypeptides can be cloned, expanded, and transferred into other vectors or effector

cells for use in adoptive immunotherapy. In particular, T cells may be transfected with the appropriate genes to express the variable domains from tumor specific monoclonal antibodies as the extracellular recognition elements and joined to the T cell receptor signaling chains, resulting in T cell activation, specific lysis, and cytokine release. This enables the T cell to redirect its specificity in an MHC-independent manner. See for example, Eshhar, Z., *Cancer Immunol Immunother*, 45(3-4):131-6, 1997 and Hwu, P., et al, *Cancer Res*, 55(15):3369-73, 1995. Another embodiment may include the transfection of tumor antigen specific alpha and beta T cell receptor chains into alternate T cells, as in Cole, DJ, et al, *Cancer Res*, 55(4):748-52, 1995.

In further embodiments, syngeneic or autologous dendritic cells may be pulsed with peptides corresponding to at least an immunogenic portion of a polypeptide disclosed herein. The resulting antigen-specific dendritic cells may either be transferred into a patient, or employed to stimulate T cells to provide antigen-specific T cells which may, in turn, be administered to a patient. The use of peptide-pulsed dendritic cells to generate antigen-specific T cells and the subsequent use of such antigen-specific T cells to eradicate tumors in a murine model has been demonstrated by Cheever et al. (*Immunological Reviews, 157*:177, 1997).

Additionally, vectors expressing the disclosed polynucleotides may be introduced into stem cells taken from the patient and clonally propagated *in vitro* for autologous transplant back into the same patient.

In one specific embodiment, cells of the immune system, such as T cells, may be isolated from the peripheral blood of a patient, using a commercially available cell separation system, such as CellPro Incorporated's (Bothell, WA) CEPRATE™ system (see U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). The separated cells are stimulated with one or more of the immunoreactive polypeptides contained within a delivery vehicle, such as a microsphere, to provide antigen-specific T cells. The population of tumor antigen-specific T cells is then expanded using standard techniques and the cells are administered back to the patient.

Polypeptides of the present invention may also, or alternatively, be used to generate binding agents, such as antibodies or fragments thereof, that are capable of detecting metastatic human breast tumors. Binding agents of the present invention may generally be prepared using methods known to those of ordinary skill in the art, including the representative procedures described herein. Binding agents are capable of differentiating between patients with and without breast cancer, using the representative assays described herein. In other words, antibodies or other binding agents raised against a breast tumor protein, or a suitable portion thereof, will generate a signal indicating the presence of primary or metastatic breast cancer in at least about 20% of patients afflicted with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without primary or metastatic breast cancer. Suitable portions of such breast tumor proteins are portions that are able to generate a binding agent that indicates the presence of primary or metastatic breast cancer in substantially all (*i.e.*, at least about 80%, and preferably at least about 90%) of the patients for which breast cancer would be indicated using the full length protein, and that indicate the absence of breast cancer in substantially all of those samples that would be negative when tested with full length protein. The representative assays described below, such as the two-antibody sandwich assay, may generally be employed for evaluating the ability of a binding agent to detect metastatic human breast tumors.

The ability of a polypeptide prepared as described herein to generate antibodies capable of detecting primary or metastatic human breast tumors may generally be evaluated by raising one or more antibodies against the polypeptide (using, for example, a representative method described herein) and determining the ability of such antibodies to detect such tumors in patients. This determination may be made by assaying biological samples from patients with and without primary or metastatic breast cancer for the presence of a polypeptide that binds to the generated antibodies. Such test assays may be performed, for example, using a representative procedure described below. Polypeptides that generate antibodies capable of detecting at least 20% of primary or metastatic breast tumors by such procedures are

considered to be useful in assays for detecting primary or metastatic human breast tumors. Polypeptide specific antibodies may be used alone or in combination to improve sensitivity.

Polypeptides capable of detecting primary or metastatic human breast tumors may be used as markers for diagnosing breast cancer or for monitoring disease progression in patients. In one embodiment, breast cancer in a patient may be diagnosed by evaluating a biological sample obtained from the patient for the level of one or more of the above polypeptides, relative to a predetermined cut-off value. As used herein, suitable "biological samples" include blood, sera and urine.

The level of one or more of the above polypeptides may be evaluated using any binding agent specific for the polypeptide(s). A "binding agent," in the context of this invention, is any agent (such as a compound or a cell) that binds to a polypeptide as described above. As used herein, "binding" refers to a noncovalent association between two separate molecules (each of which may be free (*i.e.*, in solution) or present on the surface of a cell or a solid support), such that a "complex" is formed. Such a complex may be free or immobilized (either covalently or noncovalently) on a support material. The ability to bind may generally be evaluated by determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind" in the context of the present invention when the binding constant for complex formation exceeds about 10^3 L/mol. The binding constant may be determined using methods well known to those of ordinary skill in the art.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome with or without a peptide component, an RNA molecule or a peptide. In a preferred embodiment, the binding partner is an antibody, or a fragment thereof. Such antibodies may be polyclonal, or monoclonal. In addition, the antibodies may be single chain, chimeric, CDR-grafted or humanized. Antibodies may be prepared by the methods described herein and by other methods well known to those of skill in the art.

There are a variety of assay formats known to those of ordinary skill in the art for using a binding partner to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In a preferred embodiment, the assay involves the use of binding partner immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a second binding partner that contains a reporter group. Suitable second binding partners include antibodies that bind to the binding partner/polypeptide complex. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding partner after incubation of the binding partner with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding partner is indicative of the reactivity of the sample with the immobilized binding partner.

The solid support may be any material known to those of ordinary skill in the art to which the antigen may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the antigen and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as

polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see, e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a second antibody (containing a reporter group) capable of binding to a different site on the polypeptide is added. The amount of second antibody that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is that period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with breast cancer. Preferably, the contact time is sufficient to achieve a level of binding that is

at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include enzymes (such as horseradish peroxidase), substrates, cofactors, inhibitors, dyes, radionuclides, luminescent groups, fluorescent groups and biotin. The conjugation of antibody to reporter group may be achieved using standard methods known to those of ordinary skill in the art.

The second antibody is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound second antibody is then removed and bound second antibody is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of breast cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without breast cancer.

In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for breast cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for breast cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the antibody is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized antibody as the sample passes through the membrane. A second, labeled antibody then binds to the antibody-polypeptide complex as a solution containing the second antibody flows through the membrane. The detection of bound second antibody may then be performed as described above. In the strip test format, one end of the membrane to which antibody is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second antibody and to the area of immobilized antibody. Concentration of second antibody at the area of immobilized antibody indicates the presence of breast cancer. Typically, the concentration of second antibody at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of antibody immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level

of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1 μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the antigens or antibodies of the present invention. The above descriptions are intended to be exemplary only.

In another embodiment, the above polypeptides may be used as markers for the progression of breast cancer. In this embodiment, assays as described above for the diagnosis of breast cancer may be performed over time, and the change in the level of reactive polypeptide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, breast cancer is progressing in those patients in whom the level of polypeptide detected by the binding agent increases over time. In contrast, breast cancer is not progressing when the level of reactive polypeptide either remains constant or decreases with time.

Antibodies for use in the above methods may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In one such technique, an immunogen comprising the antigenic polypeptide is initially injected into any of a wide variety of mammals (*e.g.*, mice, rats, rabbits, sheep and goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may

then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for the antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol.* *6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Monoclonal antibodies of the present invention may also be used as therapeutic reagents, to diminish or eliminate breast tumors. The antibodies may be used on their own (for instance, to inhibit metastases) or coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides,

differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number

of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous,

intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

Diagnostic reagents of the present invention may also comprise at least a portion of a polynucleotide disclosed herein. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify breast tumor-specific cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for a polynucleotide encoding a breast tumor protein of the present invention. The presence of the amplified cDNA is then detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes specific for a polynucleotide encoding a breast tumor protein of the present invention may be used in a hybridization assay to detect the presence of an inventive polypeptide in a biological sample.

As used herein, the term "oligonucleotide primer/probe specific for a polynucleotide" means an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the polynucleotide in question, or an oligonucleotide sequence that is anti-sense to a sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to the polynucleotide in question. Oligonucleotide primers and/or probes which may be usefully employed in the inventive diagnostic methods preferably have at least about 10-40 nucleotides. In a preferred embodiment, the oligonucleotide primers comprise at least about 10 contiguous nucleotides of a polynucleotide disclosed herein or that is anti-sense to a polynucleotide sequence disclosed herein. Preferably, oligonucleotide probes for use in the inventive diagnostic methods comprise at least about 15 contiguous oligonucleotides of a polynucleotide that encodes one of the polypeptides disclosed herein or that is anti-sense to a sequence that encodes one of the polypeptides disclosed herein. Techniques for both PCR based assays and hybridization assays are

well known in the art (see, for example, Mullis *et al. Ibid*; Ehrlich, *Ibid*). Primers or probes may thus be used to detect breast tumor-specific sequences in biological samples, including blood, urine and/or breast tumor tissue.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

ISOLATION AND CHARACTERIZATION OF BREAST TUMOR POLYPEPTIDES

This Example describes the isolation of breast tumor polypeptides from a breast tumor cDNA library.

A human breast tumor cDNA expression library was constructed from a pool of breast tumor poly A^+ RNA from three patients using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, breast tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A^+ RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the NotI/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BstX I adaptors (Invitrogen, Carlsbad, CA) and digested with NotI. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA 94303), the cDNA was ligated into the EcoRI/NotI site of pCDNA3.1 (Invitrogen, Carlsbad, CA) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure. a normal human breast cDNA expression library was prepared from a pool of four normal breast tissue specimens. The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The breast tumor library contained 1.14×10^7 independent colonies, with more than 90% of clones having a visible insert and the average insert size being 936 base pairs. The normal breast cDNA library contained 6×10^6 independent colonies, with 83% of clones having inserts and the average insert size being 1015 base pairs. Sequencing analysis showed both libraries to contain good complex cDNA clones that were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination sequencing.

cDNA library subtraction was performed using the above breast tumor and normal breast cDNA libraries, as described by Hara *et al.* (*Blood*, *84*:189-199, 1994) with some modifications. Specifically, a breast tumor-specific subtracted cDNA library was generated as follows. Normal breast cDNA library (70 μg) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 μl of H_2O, heat-denatured and mixed with 100 μl (100 μg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA), the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50 μl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μl H_2O to form the driver DNA.

To form the tracer DNA, 10 μg breast tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H_2O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 ^{0}C water bath and

incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 µl H_2O, mixed with 8 µl driver DNA and 20 µl of 2 x hybridization buffer, and subjected to a hybridization at 68 ^{0}C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK$^+$ (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax *E. coli* DH10B cells by electroporation to generate a breast tumor specific subtracted cDNA library.

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted breast tumor specific library and characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Thirty-eight distinct cDNA clones were found in the subtracted breast tumor-specific cDNA library. The determined 3' cDNA sequences for 14 of these clones are provided in SEQ ID NO: 1-14, with the corresponding 5' cDNA sequences being provided in SEQ ID NO: 15-28, respectively. The determined one strand (5' or 3') cDNA sequences for the remaining clones are provided in SEQ ID NO: 29-52. Comparison of these cDNA sequences with known sequences in the gene bank using the EMBL and GenBank databases (Release 97) revealed no significant homologies to the sequences provided in SEQ ID NO: 3, 10, 17, 24 and 45-52. The sequences provided in SEQ ID NO: 1, 2, 4-9, 11-16, 18-23, 25-41, 43 and 44 were found to show at least some degree of homology to known human genes. The sequence of SEQ ID NO: 42 was found to show some homology to a known yeast gene.

cDNA clones isolated in the breast subtraction described above were colony PCR amplified and their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using microarray technology (Synteni, Fremont, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and

fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity.

Data was analyzed using GEMTOOLS Software. Twenty one distinct cDNA clones were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested. The determined partial cDNA sequences for these clones are provided in SEQ ID NO: 53-73. Comparison of the sequences of SEQ ID NO: 53, 54 and 68-71 with those in the gene bank as described above, revealed some homology to previously identified human genes. No significant homologies were found to the sequences of SEQ ID NO: 55-67, 72 (referred to as JJ 9434) and 73 (referred to as B535S). In further studies, full length cDNA sequences were obtained for the clones 1016F8 (SEQ ID NO: 56; also referred to as B511S) and 1016D12 (SEQ ID NO: 61; also referred to as B532S), and an extended cDNA sequence was obtained for 1012H8 (SEQ ID NO: 64; also referred to as B533S). These cDNA sequences are provided in SEQ ID NO: 95-97, respectively, with the corresponding predicted amino acid sequences for B511S and B532S being provided in SEQ ID NO: 98 and 99, respectively.

Analysis of the expression of B511S in breast tumor tissues and in a variety of normal tissues (skin, PBMC, intestine, breast, stomach, liver, kidney, fetal tissue, adrenal gland, salivary gland, spinal cord, large intestine, small intestine, bone marrow, brain, heart, colon and pancreas) by microarray, northern analysis and real time PCR, demonstrated that B511S is over-expressed in breast tumors, and normal breast, skin and salivary gland, with expression being low or undetectable in all other tissues tested.

Analysis of the expression of B532S in breast tumor tissue and in a variety of normal tissues (breast, PBMC, esophagus, HMEC, spinal cord, bone, thymus, brain, bladder, colon, liver, lung, skin, small intestine, stomach, skeletal muscle, pancreas, aorta, heart, spleen, kidney, salivary gland, bone marrow and adrenal gland) by microarray, Northern analysis and real time PCR, demonstrated that

B532S is over-expressed in 20-30% of breast tumors with expression being low or undetectable in all other tissues tested.

In a further experiment, cDNA fragments were obtained from two subtraction libraries derived by conventional subtraction, as described above and analyzed by DNA microarray. In one instance the tester was derived from primary breast tumors, referred to as Breast Subtraction 2, or BS2. In the second instance, a metastatic breast tumor was employed as the tester, referred to as Breast Subtraction 3, or BS3. Drivers consisted of normal breast.

cDNA fragments from these two libraries were submitted as templates for DNA microarray analysis, as described above. DNA chips were analyzed by hybridizing with fluorescent probes derived from mRNA from both tumor and normal tissues. Analysis of the data was accomplished by creating three groups from the sets of probes, referred to as breast tumor/mets, normal non-breast tissues, and metastatic breast tumors. Two comparisons were performed using the modified Gemtools analysis. The first comparison was to identify templates with elevated expression in breast tumors. The second was to identify templates not recovered in the first comparison that yielded elevated expression in metastatic breast tumors. An arbitrary level of increased expression (mean of tumor expression versus the mean of normal tissue expression) was set at approximately 2.2.

In the first round of comparison to identify over-expression in breast tumors, two novel gene sequences were identified, hereinafter referred to as B534S and B538S (SEQ ID NO: 89 and 90, respectively), together with six sequences that showed some degree of homology to previously identified genes (SEQ ID NO: 74-79). The sequences of SEQ ID NO: 75 and 76 were subsequently determined to be portions of B535S (SEQ ID NO: 73). In a second comparison to identify elevated expression in metastatic breast tumors, five novel sequences were identified, hereinafter referred to as B535S, B542S, B543S, P501S and B541S (SEQ ID NO: 73 and 91-94, respectively), as well as nine gene sequences that showed some homology to known genes (SEQ ID NO: 80-88). Clone B534S and B538S (SEQ ID NO: 89 and

90) were shown to be over-expressed in both breast tumors and metastatic breast tumors.

In a subsequent series of studies, 457 clones from Breast Subtraction 2 were analyzed by microarray on Breast Chip 3. As described above, a first comparison to identify over-expression in breast tumors over normal non-breast tissues was performed. This analysis yielded six cDNA clones that demonstrated elevated expression in breast tumor over normal non-breast tissues. Two of these clones, referred to as 1017C2 (SEQ ID NO: 102) and B546S (SEQ ID NO: 107) do not share significant homology to any known genes. Clone B511S also showed over-expression in breast tumor, which was previously described as 1016F8, with the determined cDNA sequence provided in SEQ ID NO: 95 and the predicted amino acid sequence provided in SEQ ID NO: 98. The remaining four clones over-expressed in breast tumor were found to share some degree of homology to Tumor Expression Enhanced Gene (SEQ ID NO: 103 and 104) Stromelysin-3 (SEQ ID NO: 105) or Collagen (SEQ ID NO: 106).

In the second comparison to determine genes with elevated expression in metastatic breast tumors over non-breast normal tissues, a profile similar to the first comparison was derived. The two putatively novel clones, 1017C2 and B546S, SEQ ID NO: 102 and 107, respectively, were overexpressed in metastatic breast tumors. In addition, Tumor Expression Enhanced Gene and B511S also showed elevated expression in metastatic breast tumors.

As described in U.S. Patent Application No. 08/806,099, filed February 25, 1997, the antigen P501S was isolated by subtracting a prostate tumor cDNA library with a normal pancreas cDNA library and with three genes found to be abundant in a previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. The determined full-length cDNA sequence for P501S is provided in SEQ ID NO: 100, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 101. Expression of P501S in breast tumor was examined by microarray analysis. Over-expression was found in prostate tumor, breast tumor

and metastatic breast tumor, with negligible to low expression being seen in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

Example 2

GENERATION OF HUMAN CD8+ CYTOTOXIC T-CELLS THAT RECOGNIZE ANTIGEN PRESENTING CELLS EXPRESSING BREAST TUMOR ANTIGENS

This Example illustrates the generation of T cells that recognize target cells expressing the antigen B511S, also known as 1016-F8 (SEQ ID NO: 56). Human CD8+ T cells were primed *in-vitro* to the B511S gene product using dendritic cells infected with a recombinant vaccinia virus engineered to express B511S as follows (also see Yee et al., Journal of Immunology (1996) 157 (9):4079-86). Dendritic cells (DC) were generated from peripheral blood derived monocytes by differentiation for 5 days in the presence of 50 μg/ml GMCSF and 30 μg/ml IL-4. DC were harvested, plated in wells of a 24-well plate at a density of 2 x 10^5 cells/well and infected for 12 hours with B511S expressing vaccinia at a multiplicity of infection of 5. DC were then matured overnight by the addition of 3 μg/ml CD40-Ligand and UV irradiated at 100μW for 10 minutes. CD8+ T cells were isolated using magnetic beads, and priming cultures were initiated in individual wells (typically in 24 wells of a 24-well plate) using 7 x 10^5 CD8+ T cells and 1 x 10^6 irradiated CD8-depleted PBMC. IL-7 at 10 ng/ml was added to cultures at day 1. Cultures were re-stimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with B511S and the costimulatory molecule B7.1. Cultures were supplemented at day 1 with 15 I.U. of IL-2. Following 4 such stimulation cycles, CD8+ cultures were tested for their ability to specifically recognize autologous fibroblasts transduced with B511S using an interferon-γ Elispot assay (see Lalvani et al J. Experimental Medicine (1997) 186:859-965). Briefly, T cells from individual microcultures were added to 96-well Elispot plates that contained autologous fibroblasts transduced to express either B511S or as a negative control

antigen EGFP, and incubated overnight at 37° C; wells also contained IL-12 at 10 ng/ml. Cultures were identified that specifically produced interferon-γ only in response to B511S transduced fibroblasts; such lines were further expanded and also cloned by limiting dilution on autologous B-LCL retrovirally transduced with B511S. Lines and clones were identified that could specifically recognize autologous B-LCL transduced with B511S but not autologous B-LCL transduced with the control antigens EGFP or HLA-A3. An example demonstrating the ability of human CTL cell lines derived from such experiments to specifically recognize and lyse B511S expressing targets is presented in Figure 1.

Example 3
SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on an Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

CLAIMS

1. An isolated polypeptide comprising an immunogenic portion of a breast protein or a variant thereof, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-97, 102 and 107; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

2. The isolated polypeptide of claim 1, wherein the polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 98,99 and 101.

3. An isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide of any one of claims 1 and 2.

4. An isolated polynucleotide comprising a sequence provided in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-97, 102 and 107.

5. An expression vector comprising a polynucleotide according to any one of claims 3 and 4.

6. A host cell transformed with the expression vector of claim 5.

7. The host cell of claim 6 wherein the host cell is selected from the group consisting of *E. coli*, yeast and mammalian cell lines.

8. A pharmaceutical composition comprising the polypeptide of claim 1 and a physiologically acceptable carrier.

9. A vaccine comprising the polypeptide of claim 1 and a non-specific immune response enhancer.

10. The vaccine of claim 9 wherein the non-specific immune response enhancer is an adjuvant.

11. A vaccine comprising an isolated polynucleotide of any one of claims 3 and 4, and a non-specific immune response enhancer.

12. The vaccine of claim 11 wherein the non-specific immune response enhancer is an adjuvant.

13. A pharmaceutical composition for the treatment of breast cancer comprising a polypeptide and a physiologically acceptable carrier, the polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

14. A vaccine for the treatment of breast cancer comprising a polypeptide and a non-specific immune response enhancer, said polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

15. The vaccine of claim 14 wherein the non-specific immune response enhancer is an adjuvant.

16. A vaccine for the treatment of breast cancer comprising a polynucleotide and a non-specific immune response enhancer, the polynucleotide

comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 and 103-106; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

17. The vaccine of claim 16, wherein the non-specific immune response enhancer is an adjuvant.

18. A pharmaceutical composition according to any one of claims 8 and 13, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

19. A vaccine according to any one of claims 9, 11, 14 or 16, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

20. A fusion protein comprising at least one polypeptide according to claim 1.

21. A pharmaceutical composition comprising a fusion protein according to claim 20 and a physiologically acceptable carrier.

22. A vaccine comprising a fusion protein according to claim 20 and a non-specific immune response enhancer.

23. The vaccine of claim 22 wherein the non-specific immune response enhancer is an adjuvant.

24. A pharmaceutical composition according to claim 21, for use in manufacture of a medicament for inhibiting the development of breast cancer in a patient.

25. A vaccine according to claim 22, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

26. A method for detecting breast cancer in a patient, comprising:

(a) contacting a biological sample from a patient with a binding agent which is capable of binding to a polypeptide, the polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence provided in SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions; and

(b) detecting in the sample a protein or polypeptide that binds to the binding agent, thereby detecting breast cancer in the patient.

27. The method of claim 26 wherein the binding agent is a monoclonal antibody.

28. The method of claim 27 wherein the binding agent is a polyclonal antibody.

29. A method for monitoring the progression of breast cancer in a patient, comprising:

(a) contacting a biological sample from a patient with a binding agent that is capable of binding to a polypeptide, said polypeptide comprising an immunogenic portion of a breast protein, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence provided in SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions;

(b) determining in the sample an amount of a protein or polypeptide that binds to the binding agent;

(c) repeating steps (a) and (b); and

(d) comparing the amount of polypeptide detected in steps (b) and (c) to monitor the progression of breast cancer in the patient.

30. A monoclonal antibody that binds to a polypeptide comprising an immunogenic portion of a breast protein or a variant of said protein that differs only in conservative substitutions and/or modifications, wherein said protein comprises an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NOS: 3, 10, 17, 24, 45-52, 55-67, 72, 73, 89-97, 102 and 107; (b) complements of said nucleotide sequences; and (c) sequences that hybridize to a sequence of (a) or (b) under moderately stringent conditions.

31. A monoclonal antibody according to claim 30, for use in the manufacture of a medicament for inhibiting the development of breast cancer in a patient.

32. The monoclonal antibody of claim 31 wherein the monoclonal antibody is conjugated to a therapeutic agent.

33. A method for detecting breast cancer in a patient comprising:

(a) contacting a biological sample from a patient with at least two oligonucleotide primers in a polymerase chain reaction, wherein at least one of the oligonucleotides is specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NO: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-97,100 and 102-107 under moderately stringent conditions; and

(b) detecting in the sample a polynucleotide sequence that amplifies in the presence of the oligonucleotide primers, thereby detecting breast cancer.

34. The method of claim 33, wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NOS: 1-97, 100 and 102-107.

35. A diagnostic kit comprising:

(a) one or more monoclonal antibodies of claim 30; and

(b) a detection reagent.

36. A diagnostic kit comprising:

(a) one or more monoclonal antibodies that bind to a polypeptide encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71,74-88 and 103-106, complements of said sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1, 2, 4-9, 11-16, 18-23, 25-44, 53, 54, 68-71, 74-88 or 103-106 under moderately stringent conditions; and

(b) a detection reagent.

37. The kit of claims 35 or 36 wherein the monoclonal antibodies are immobilized on a solid support.

38. The kit of claim 37 wherein the solid support comprises nitrocellulose, latex or a plastic material.

39. The kit of claims 35 or 36 wherein the detection reagent comprises a reporter group conjugated to a binding agent.

40. The kit of claim 39 wherein the binding agent is selected from the group consisting of anti-immunoglobulins, Protein G, Protein A and lectins.

41. The kit of claim 39 wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.

42. A diagnostic kit comprising at least two oligonucleotide primers, at least one of the oligonucleotide primers being specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107 complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions.

43. A diagnostic kit of claim 42 wherein at least one of the oligonucleotide primers comprises at least about 10 contiguous nucleotides of a polynucleotide comprising a sequence selected from SEQ ID NOS: 1-97, 100 and 102-107.

44. A method for detecting breast cancer in a patient, comprising:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions; and

(c) detecting in the sample a polynucleotide sequence that hybridizes to the oligonucleotide probe, thereby detecting breast cancer in the patient.

45. The method of claim 44 wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97, 100 and 102-107.

46. A diagnostic kit comprising an oligonucleotide probe specific for a polynucleotide encoding a polypeptide comprising an immunogenic portion of a breast protein, said protein comprising an amino acid sequence encoded by a polynucleotide comprising a sequence selected from the group consisting of nucleotide sequences recited in SEQ ID NOS: 1-97, 100 and 102-107, complements of said nucleotide sequences, and sequences that hybridize to a sequence of SEQ ID NO: 1-97, 100 and 102-107 under moderately stringent conditions.

47. The diagnostic kit of claim 46, wherein the oligonucleotide probe comprises at least about 15 contiguous nucleotides of a polynucleotide comprising a sequence selected from the group consisting of SEQ ID NOS: 1-97,100 and 102-107.

48. A method for treating breast cancer in a patient, comprising the steps of:

(a) obtaining peripheral blood cells from the patient;

(b) incubating the cells in the presence of at least one polypeptide of any one of claims 1 and 2, such that T cells proliferate; and administering the proliferated T cells to the patient.

49. A method for treating breast cancer in a patient, comprising the steps of:

(a) obtaining peripheral blood cells from the patient;

(b) incubating the cells in the presence of at least one polynucleotide of any one of claims 3 and 4, such that T cells proliferate; and

(c) administering the proliferated T cells to the patient.

50. The method of any one of claims 48 and 49 wherein the step of incubating the cells is repeated one or more times.

51. The method of any one of claims 48 and 49 wherein step (a) further comprises separating the T cells from the peripheral blood cells and the cells incubated in step (b) are the T cells.

52. The method of any one of claims 48 and 49 wherein step (a) further comprises separating CD4+ cells or CD8+ cells from the peripheral blood cells and the cells proliferated in step (b) are CD4+ or CD8+ T cells.

53. The method of any one of claims 48 and 49 wherein step (b) further comprises cloning at least one T cell that proliferated in the presence of the polypeptide.

54. A composition for the treatment of breast cancer in a patient, comprising T cells proliferated in the presence of a polypeptide of any one of claims 1 and 2, in combination with a pharmaceutically acceptable carrier.

55. A composition for the treatment of breast cancer in a patient comprising T cells proliferated in the presence of a polynucleotide of any one of claims 3 and 4, in combination with a pharmaceutically acceptable carrier.

56. A method for treating breast cancer in a patient, comprising the steps of:

(a) incubating antigen presenting cells in the presence of at least one polypeptide of any one of claims 1 and 2; and

(b) administering to the patient the incubated antigen presenting cells.

57. A method for treating breast cancer in a patient, comprising the steps of:

(a) incubating antigen presenting cells in the presence of at least one polynucleotide of any one of claims 3 and 4; and

(b) administering to the patient the incubated antigen presenting

cells.

58. The method of claims 56 or 57 wherein the antigen presenting cells are selected from the group consisting of dendritic cells, macrophage cells, monocyte cells, fibroblast cells, B-cells or combinations thereof.

59. A composition for the treatment of breast cancer in a patient, comprising antigen presenting cells incubated in the presence of a polypeptide of any one of claims 1 and 2, in combination with a pharmaceutically acceptable carrier.

60. A composition for the treatment of breast cancer in a patient, comprising antigen presenting cells incubated in the presence of a polynucleotide of any one of claims 3 and 4, in combination with a pharmaceutically acceptable carrier.

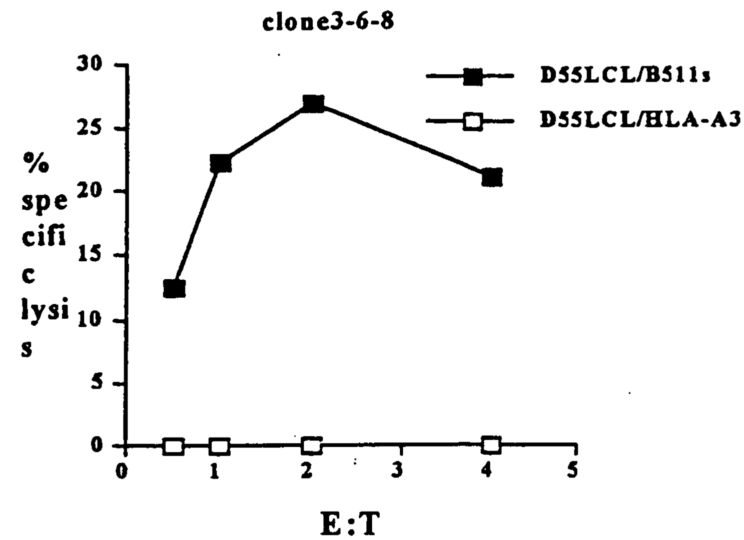

FIGURE 1A

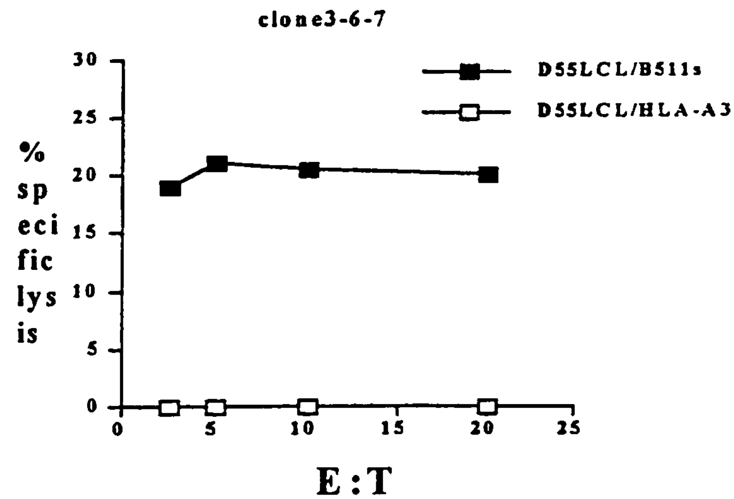

FIGURE 1B

Figure 1: Specific lytic activity of B511s-specific CTL clones 3-6-8 and 3-6-7 measured on autologous LCL transduced with B511s (filled squares) or HLA-A3 (open squares). Each data point is the average of triplicate measurements.

FIGS. 1A AND 1B

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Reed, Steven G.
Xu, Jiangchun
Dillon, Davin C.

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ccacngatgg gggtcatttt tntcnnttag ccagtttgtg nagttccgtt attganaaaa 420
ccan 424

<210> 12
<211> 426
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(426)
<223> n = A,T,C or G

<400> 12
tttttttttt ttttncttaa aagcttttat ctcctgctta cattacccat ctgttcttgc 60
atgttgtctg ctttttccac tagagccctt aacaacttaa tcatggttat tttaagggct 120
ctaataattc cnaaactggt atcataaata agtctcgttc tnatgcttgt tttctctcta 180
tcacactgtg ttngttgctt tttnacatgc tttgtaattt ttggctgaaa gctgaaaaat 240
nacatacctg gttntacaac ctgaggtaan cagccttnta gtgtgaggtt ttatatntta 300
ctggctaaga gctnggcnct gttnantant tgttgtanct ntatatgcca naggctttna 360
tttccnctng tgtccttgct tnagtacccc attnttttag gggttcccta naaactctat 420
ctnaat 426

<210> 13
<211> 419
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(419)
<223> n = A,T,C or G

<400> 13
tttttttttt tttttnagat agactctcac tctttcgccc aggctggagt gcagtggcgc 60
aatcaaggct cactgcaacc tctgccttat aaagcatttn ctaaaggtac aagctaaatt 120
ttaaaaatat ctctncacaa ctaatgtata acaaaaatta gttctacctc ataaacncnt 180
ggctcagccc tcgnaacaca tttccctgtt ctcaactgat gaacactcca naaacagaac 240
anatntaagc ttttccaggc ccagaaaagc tcgcgagggg atttgctntg tgtgtgacac 300
acttgccacc ctgtggcagc acagctccac acntgctttg ggccgcattt gcaagttctc 360
tgtaancccc ctgnaagacc cggatcagct gggtngaaat tgcangcnct cttttggca 419

<210> 14
<211> 400
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(400)
<223> n = A,T,C or G

<400> 14
aanccattgc caagggtatc cggaggattg tggctgtcac aggtnccgag gcccanaagg 60
ccctcaggaa agcaaagagc ttgaaaaatg tctctctgtc atggaagccn aagtgaaggc 120
tcanactgct ccaacaagga tntgcanagg gagatcgcta accttggaga ggccctggcc 180
actgcagtcn tcccccantg gcagaaggat gaattgcggg agactctcan atcccttang 240
gaaggtcgtg gatnacttgg accgagcctc nnaagccaat ntccagaaca agtgttggag 300
aagacaaagc anttcatcga cgccaacccc naccggcctc tnttctcctg ganattgana 360
gcggcgcccc cgcccagggc cttaataanc cntgaagctn 400

<210> 15
<211> 395
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(395)
<223> n = A,T,C or G

<400> 15
tgctttgctg cgtccaggaa gattagatng aanaatacat attgatttgc caaatgaaca 60
agcgagatta gacntactga anatccatgc aggtcccatt acaaagcatg gtgaaataga 120
tgatgaagca attgtgaagc tatcggatgg ctttnatgga gcagatctga gaaatgtttg 180
tactgaagca ggtatgttcg caattcgtgc tgatcatgat tttgtagtac aggaagactt 240
catgaaagcn gtcagaanag tggctnattc tnaaagctgg agtctaaatt ggacnacnac 300
ctntgtattt actgttggan ttttgatgct gcatgacaga ttttgcttan tgtaaaaatn 360
aagttcaaga aaattatgtt agttttggcc attat 395

<210> 16
<211> 404
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(404)
<223> n = A,T,C or G

<400> 16
ccaccactaa aatcctggct gagccctacn agtacctgtg cccctccccc aggacgagat 60
nagggcacac cctttaagtn aggtgacagg tcacctttaa gtgaggacag tcagctnaat 120
ttcacctctt gggcttgagt acctggttct cgtgccctga ggcgacnctn agccctgcag 180
ctnccatgta cgtgctgcca atngtcttga tcttctccac gccnctnaac ttgggcttca 240
gtaggagctg caggcnagaa ngaagcggtt aacagcgcca ctccatagcc gcagccnggc 300
tgcccctgct tctcaaggag gggtgtgggg ttcctccacc atcgccgccc ttgcaaacac 360
ntctcanggc ttccctnccg gctnancgca ngacttaagc atgg 404

<210> 17

<211> 360
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(360)
<223> n = A,T,C or G

<400> 17
ggccagaagc tttccacaaa ccagtgaagg tggcagcaaa gaaagcctct tagacnagga 60
gctggcagca gctgctatct ngatngacng cagaaaccaa ccactaattc agcaaacaca 120
acctcatacc tnaccgcttc cctttnaatg gccttcggtg tgtgcgcaca tgggcacgtg 180
cggggagaac catacttatt cccctnttcc cggcctacca cctctnctcc cccttctctt 240
ctctncaatt actntctccn ctgctttntt ctnancacta ctgctngtnt cnanagccng 300
cccgcaatta cctggcaaaa ctcgcgaccc ttcgggcagc gctaaanaat gcacatttac 360

<210> 18
<211> 316
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(316)
<223> n = A,T,C or G

<400> 18
atacatatac acatatatga ttttagatag agccatatac ctngaagtag tanatttgtt 60
tgtgtgtata tgtatgtgtc tactcatttt aaataaactt gtgatagaga tgtaattntg 120
agccagtttt tcatttgctt aaatnactca ccaagtaact aattaagttn tctttactct 180
taatgttnag tagtgagatt ctgttgaagg tgatattaaa aaccattcta tattaattaa 240
cattcatgtt gtttttttaaa agcttatttg aaatcnaatt atgattattt ttcataccag 300
tcgatnttat gtangt 316

<210> 19
<211> 350
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(350)
<223> n = A,T,C or G

<400> 19
aagggatgca nataatgctg tgtatgagct tgatggaaaa gaactctgta gtgaaagggt 60
tactattgaa catgctnggg ctcggtcacg aggtggaaga ggtagaggac gatactctga 120
ccgttttagt agtcgcagac ctcgaaatga tagacgaaat gctccacctg taagaacaga 180
anatcgtctt atagttgaga atttatcctc aagagtcagc tggcaggttt gttganatac 240
agttttgagt tnttttgatg tggcttttta aaaaagttat gggttactna tgttatattg 300
ttttattaaa agtagttttn aattaatgga tntgatggaa ttgttgtttt 350

<210> 20
<211> 367

<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(367)
<223> n = A,T,C or G

<400> 20
gntnnncnca agatcctnct ntccccengg gcngccccnc cnccngtnat naccggtttn 60
ntaanatcnn gccgcncccg aagtctcnct nntgccgaga tgncccttat ncncnnatgn 120
ncaattntga cctnnggcga anaatggcng nngtgtatca gtntccnctc tgnggnctct 180
tagnatctga ccactangac ccnctatcct ctcaaaccct gtanncngcc ctaatttgtg 240
ccaattagtg catgntanag cntcctggcc cagatggcnt ccatatcctg gtncggcttc 300
cgcccctacc angncatccn catctactag agcttatccg ctncntgngg cgcaccggnt 360
ccccnct 367

<210> 21
<211> 366
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(366)
<223> n = A,T,C or G

<400> 21
cccaacacaa tggtctaagt anaactgtat tgctctgtag tatagttcca cattggcaac 60
ctacaatggg aaaatccata cataagtcag ttacttcctn atgagctttc tccttctgaa 120
tcctttatct tctgaagaaa gtacacacct tggtnatgat atctttgaat tgcccttctt 180
tccaggcatc agttggatga ttcatcatgg taattatggc attatcatat tcttcatact 240
tgtcatacga aaacaccagt tctgcccnna gatgagcttg ttctgcagct cttagcacct 300
tgggaatatt cactctagac cagaaacagc tcccggtgct ccctcatttt ctgaggctta 360
aatttn 366

<210> 22
<211> 315
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(315)
<223> n = A,T,C or G

<400> 22
acttaatgca atctctggag gataatttgg atcaagaaat aaagaanaaa tgaattagga 60
gaagaaatna ctgggtnata tttcaatatt ttagaacttt aanaatgttg actatgattt 120
caatatattt gtnaaaactg agatacangt ttgacctata tctgcatttt gataattaaa 180
cnaatnnatt ctatttnaat gttgtttcag agtcacagca cagactgaaa ctttttttga 240
atacctnaat atcacacttn tncttnnaat gatgttgaag acaatgatga catgccttna 300
gcatataatg tcgac 315

<210> 23

<211> 202
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(202)
<223> n = A,T,C or G

<400> 23
actaatccag tgtggtgnaa ttccattgtg ttgggcaact caggatatta aatttatnat 60
ttaaaaattc ccaagagaaa naaactccag gccctgattg tttcactggg gaattttacc 120
aaatgttnca nnaaganatg acgctgattc tgtnaaatct ttttcagaag atagaggaga 180
acacccaccg nttcatttta tg 202

<210> 24
<211> 365
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(365)
<223> n = A,T,C or G

<400> 24
ggatttcttg cccttttctc ccttttttaag tatcaatgta tgaaatccac ctgtaccacc 60
ctttctgcca tacaaccgct accacatctg gctcctagaa cctgttttgc tttcatagat 120
ggatctcgga accnagtgtt nacttcattt ttaaacccca ttttagcaga tngtttgctn 180
tggtctgtct gtattcacca tggggcctgt acacaccacg tgtggttata gtcaaacaca 240
gtgccctcca ttgtggccac atgggagacc catnacccna tactgcatcc tgggctgatn 300
acggcactgc atctnacccg acntgggatt gaacccgggg tgggcagcng aattgaacag 360
gatca 365

<210> 25
<211> 359
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(359)
<223> n = A,T,C or G

<400> 25
gtttcctgct tcaacagtgc ttggacggaa cccggcgctc gttccccacc ccggccggcc 60
gcccatagcc agccctccgt cacctcttca ccgcaccctc ggactgcccc aaggcccccg 120
ccgccnctcc ngcgccncgc agccaccgcc gccnccncca cctctccttn gtcccgccnt 180
nacaacgcgt ccacctcgca ngttcgccng aactaccacc nggactcata ngccgccctc 240
aaccgcccga tcaacctgga gctctncccc ccgacnttaa cctttccntg tcttacttac 300
nttaaccgcc gnttattttg cttnaaaaga acttttcccc aatactttct ttcaccnnt 359

<210> 26
<211> 400
<212> DNA

<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(400)
<223> n = A,T,C or G

<400> 26
agtgaaacag tatatgtgaa aaggagtttg tgannagcta cataaaaata ttagatatct 60
ttataatttc caataggata ctcatcagtt ttgaataana gacatattct agagaaacca 120
ggtttctggt ttcagatttg aactctcaag agcttggaag ttatcactcc catcctcacg 180
acnacnaana aatctnaacn aacngaanac caatgacttt tcttagatct gtcaaagaac 240
ttcagccacg aggaaaacta tcnccctnaa tactggggac tggaaagaga gggtacagag 300
aatcacagtg aatcatagcc caagatcagc ttgcccggag ctnaagctng tacgatnatt 360
acttacaggg accacttcac agtnngtnga tnaantgccn 400

<210> 27
<211> 366
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(366)
<223> n = A,T,C or G

<400> 27
gaatttctta gaaactgaag tttactctgt tccaagatat atcttcactg tcttaatcaa 60
agggcgctng aatcatagca aatattctca tctttcaact aactttaagt agttntcctg 120
gaattttaca ttttccagaa aacactcctt tctgtatctg tgaaagaaag tgtgcctcag 180
gctgtagact gggctgcact ggacacctgc gggggactct ggctnagtgn ggacatggtc 240
agtattgatt ttcctcanac tcagcctgtg tagctntgaa agcatggaac agattacact 300
gcagttnacg tcatcccaca catcttggac tccnagaccc ggggaggtca catagtccgt 360
tatgna 366

<210> 28
<211> 402
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(402)
<223> n = A,T,C or G

<400> 28
agtgggagcc tcctccttcc ccactcagtt ctttacatcc ccgaggcgca gctgggcnaa 60
ggaagtggcc agctgcagcg cctcctgcag gcagccaacg ttcttgcctg tggcctgtgc 120
agacacatcc ttgccaccac ctttaccgtc catcangcct gacacctgct gcacccactc 180
gctngctttt aagccccgat nggctgcatt ctgggggact tgacacaggc ncgtgatctt 240
gccagcctca ttgtccaccg tgaagagcat ggcaaaaagt ctgaggggag tgcatcttga 300
anagcttcaa ggcttcattc agggccttng ctnaggcgcc nctctccatc tccnggaata 360
acnagaggct ggtnngggtn actntcaata aactgcttcg tc 402

<210> 29

<211> 175
<212> DNA
<213> Homo sapien

<400> 29
cggacgggca tgaccggtcc ggtcagctgg gtggccagtt tcagttcttc agcagaactg 60
tctcccttct tgggggccga gggcttcctg gggaagagga tgagtttgga gcggtactcc 120
ttcagccgct gcacgttggt ctgcagggac tccgtggact tgttccgcct cctcg 175

<210> 30
<211> 360
<212> DNA
<213> Homo sapien

<400> 30
ttgtatttct tatgatctct gatgggttct tctcgaaaat gccaagtgga agactttgtg 60
gcatgctcca gatttaaatc cagctgaggc tccctttgtt ttcagttcca tgtaacaatc 120
tggaaggaaa cttcacggac aggaagactg ctggagaaga gaagcgtgtt agcccatttg 180
aggtctgggg aatcatgtaa agggtaccca gacctcactt ttagttattt acatcaatga 240
gttctttcag ggaaccaaac ccagaattcg gtgcaaaagc caaacatctt ggtgggattt 300
gataaatgcc ttgggacctg gagtgctggg cttgtgcaca ggaagagcac cagccgctga 360

<210> 31
<211> 380
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(380)
<223> n = A,T,C or G

<400> 31
acgctctaag cctgtccacg agctcaatag ggaagcctgt gatgactaca gactttgcga 60
acgctacgcc atggtttatg gatacaatgc tgcctataan cgctacttca ggaagcgccg 120
agggaccnaa tgagactgag ggaagaaaaa aaatctcttt ttttctggag gctggcacct 180
gattttgtat ccccctgtnn cagcattncn gaaatacata ggcttatata caatgcttct 240
ttcctgtata ttctcttgtc tggctgcacc ccttnttccc gcccccagat tgataagtaa 300
tgaaagtgca ctgcagtnag ggtcaangga gactcancat atgtgattgt tccntnataa 360
acttctggtg tgatactttc 380

<210> 32
<211> 440
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(440)
<223> n = A,T,C or G

<400> 32
gtgtatggga gcccctgact cctcacgtgc ctgatctgtg cccttggtcc caggtcaggc 60
ccaccccctg cacctccacc tgccccagcc cctgcctctg ccccaagtgg ggccagctgc 120
cctcacttct ggggtggatg atgtgacctt cctngggga ctgcggaagg gacaagggtt 180

ccctgaagtc ttacggtcca acatcaggac caagtcccat ggacatgctg acagggtccc 240
caggggagac cgtntcanta gggatgtgtg cctggctgtg tacgtgggtg tgcagtgcac 300
gtganaagca cgtggcggct tctgggggcc atgtttgggg aaggaagtgt gcccnccacc 360
cttggagaac ctcagtcccn gtagccccct gccctggcac agcngcatnc acttcaaggg 420
caccctttgg gggttggggt 440

<210> 33
<211> 345
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(345)
<223> n = A,T,C or G

<400> 33
tattttaaca atgtttatta ttcatttatc cctctataga accaccaccc acaccgagga 60
gattatttgg agtgggtccc aacctagggc ctggactctg aaatctaact ccccacttcc 120
ctcattttgt gacttaggtg gggcatggt tcagtcagaa ctggtgtctc ctattggatc 180
gtgcagaagg aggacctagg cacacacata tggtggccac acccaggagg gttgattggc 240
aggctggaag acaaaagtct cccaataaag gcacttttac ctcaaagang gggtgggagt 300
tggtctgctg ggaatgttgt tgttggggtg gggaagantt atttc 345

<210> 34
<211> 440
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(440)
<223> n = A,T,C or G

<400> 34
tgtaattttt ttattggaaa acaaatatac aacttggaat ggattttgag gcaaattgtg 60
ccataagcag atttaagtg gctaaacaaa gtttaaaaag caagtaacaa taaaagaaaa 120
tgtttctggt acaggaccag cagtacaaaa aaatagtgta cgagtacctg gataatacac 180
ccgttttgca atagtgcaac ttttaagtac atattgttga ctgtccatag tccacgcaga 240
gttacaactc cacacttcaa caacaacatg ctgacagttc ctaaagaaaa ctactttaaa 300
aaaggcataa cccagatgtt ccctcatttg accaactcca tctnagttta gatgtgcaga 360
agggcttana ttttcccaga gtaagccnca tgcaacatgt tacttgatca attttctaaa 420
ataaggtttt aggacaatga 440

<210> 35
<211> 540
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(540)
<223> n = A,T,C or G

<400> 35

atagatggaa tttattaagc ttttcacatg tgatagcaca tagttttaat tgcatccaaa 60
gtactaacaa aaactctagc aatcaagaat ggcagcatgt tattttataa caatcaacac 120
ctgtggcttt taaaatttgg ttttcataag ataatttata ctgaagtaaa tctagccatg 180
cttttaaaaa atgctttagg tcactccaag cttggcagtt aacatttggc ataaacaata 240
ataaaacaat cacaatttaa taaataacaa atacaacatt gtaggccata atcatataca 300
gtataaggga aaaggtggta gtgttganta agcagttatt agaatagaat accttggcct 360
ctatgcaaat atgtctagac actttgattc actcagccct gacattcagt tttcaaagtt 420
aggaaacagg ttctacagta tcattttaca gtttccaaca cattgaaaac aagtagaaaa 480
tgatganttg atttttatta atgcattaca tcctcaagan ttatcaccaa cccctcaggt 540

<210> 36
<211> 555
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(555)
<223> n = A,T,C or G

<400> 36
cttcgtgtgc ttgaaaattg gagcctgccc ctcggcccat aagcccttgt tgggaactga 60
gaagtgtata tggggcccaa nctactggtg ccagaacaca gagacagcag cccantgcaa 120
tgctgtcgag cattgcaaac gccatgtgtg gaactaggag gaggaatatt ccatcttggc 180
agaaaccaca gcattggttt ttttctactt gtgtgtctgg gggaatgaac gcacagatct 240
gtttgacttt gttataaaaa tagggctccc ccacctcccc cntttctgtg tnctttattg 300
tagcantgct gtctgcaagg gagcccctan cccctggcag acananctgc ttcagtgccc 360
ctttcctctc tgctaaatgg atgttgatgc actggaggtc ttttancctg cccttgcatg 420
gcncctgctg gaggaagana aaactctgct ggcatgaccc acagtttctt gactggangc 480
cntcaaccct cttggttgaa gccttgttct gaccctgaca tntgcttggg cnctgggtng 540
gnctgggctt ctnaa 555

<210> 37
<211> 280
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(280)
<223> n = A,T,C or G

<400> 37
ccaccgacta taagaactat gccctcgtgt attcctgtac ctgcatcatc caactttttc 60
acgtggattt tgcttggatc ttggcaagaa accctaatct ccctccagaa acagtggact 120
ctctaaaaaa tatcctgact tctaataaca ttgatntcaa gaaaatgacg gtcacagacc 180
aggtgaactg ccccnagctc tcgtaaccag gttctacagg gaggctgcac ccactccatg 240
ttncttctgc ttcgctttcc cctaccccac cccccgccat 280

<210> 38
<211> 303
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(303)
<223> n = A,T,C or G

<400> 38
catcgagctg gttgtcttct tgcctgccct gtgtcgtaaa atgggggtcc cttactgcat 60
tatcaaggga aaggcaagac tgggacgtct agtccacagg aagacctgca ccactgtcgc 120
cttcacacag gtgaactcgg aagacaaagg cgctttggct nagctggtgn aagctatcag 180
gaccaattac aatgacngat acgatnagat ccgccntcac tggggtagca atgtcctggg 240
tcctaagtct gtggctcgta tcgccnagct cgaanaggcn aangctaaag aacttgccac 300
taa 303

<210> 39
<211> 300
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

<400> 39
gactcagcgg ctggtgctct tcctgtgcac aagcccagca ctccaggtcc caaggcattt 60
atcaaatccc accaagatnt ttggcttttg caccgaattc tgggtttggt tccctnaaag 120
aactcattga tgtaaatnac tnaaagtgag gtctgggtac cctttacatg attccccaga 180
cctcanatgg gctaacacgc ttctcttctc cagcagtctt cctntccgtg aagttacctt 240
ccagattgtt acatggaact gaanacaaag ggagcctcag ctngatttaa atctggagca 300

<210> 40
<211> 318
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(318)
<223> n = A,T,C or G

<400> 40
cccaacacaa tggctgagga caaatcagtt ctctgtgacc agacatgaga aggttgccaa 60
tgggctgttg ggcgaccaag gccttcccgg agtcttcgtc ctctatgagc tctcgcccat 120
gatggtgaag ctgacggaga agcacaggtc cttcacccac ttcctgacag gtgtgtgcgc 180
catcattggg ggcatgttca cagtggctgg actcatcgat tcgctcatct accactcagc 240
acgagccatc cagaaaaaaa ttgatctngg gaagacnacg tagtcaccct cggtncttcc 300
tctgtctcct ctttctcc 318

<210> 41
<211> 302
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(302)

<223> n = A,T,C or G

<400> 41
```
acttagatgg ggtccgttca ggggatacca gcgttcacat ttttcctttt aagaaagggt      60
cttggcctga atgttcccca tccggacaca ggctgcatgt ctctgtnagt gtcaaagctg     120
ccatnaccat ctcggtaacc tactcttact ccacaatgtc tatnttcact gcagggctct     180
ataatnagtc cataatgtaa atgcctggcc caagacntat ggcctgagtt tatccnaggc     240
ccaaacnatt accagacatt cctcttanat tgaaaacgga tntctttccc ttggcaaaga     300
tc                                                                    302
```

<210> 42
<211> 299
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(299)
<223> n = A,T,C or G

<400> 42
```
cttaataagt ttaaggccaa ggcccgttcc attcttctag caactgacgt tgccagccga      60
ggtttggaca tacctcatgt aaatgtggtt gtcaactttg acattcctac ccattccaag     120
gattacatcc atcgagtagg tcgaacagct agagctgggc gctccggaaa ggctattact     180
tttgtcacac agtatgatgt ggaactcttc cagcgcatag aacacttnat tgggaagaaa     240
ctaccaggtt ttccaacaca ggatgatgag gttatgatgc tnacggaacg cgtcgctna      299
```

<210> 43
<211> 305
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(305)
<223> n = A,T,C or G

<400> 43
```
ccaacaatgt caagacagcc gtctgtgaca tcccacctcg tggcctcaan atggcagtca      60
ccttcattgg caatagcaca gccntccggg agctcttcaa gcgcatctcg gagcagttca     120
ctgccatgtt ccgccggaag gccttcctcc actggtacac aggcgagggc atggacaaga     180
tggagttcac cgaggctgag agcaacatga acgacctcgt ctctnagtat cagcagtacc     240
gggatgccac cgcagaaana ggaggaggat ttcggtnagg aggccgaaga aggaggcctg     300
aggca                                                                 305
```

<210> 44
<211> 399
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(399)
<223> n = A,T,C or G

<400> 44
tttctgtggg ggaaacctga tctcgacnaa attagagaat tttgtcagcg gtatttcggc 60
tggaacagaa cgaaaacnga tnaatctctg tttcctgtat taaagcaact cgatncccag 120
cagacacagc tccnaattga ttccttcttt ngattagcac aacagggaga aagaanatgc 180
ttaacgtatt aagagccnga gactaaacag agctttgaca tgtatgctta ggaaagagaa 240
agaagcagcn gcccgcgnaa ttngaagcng tttctgttgc cntgganaaa gaatttgagc 300
ttctttatta ggccaacgaa aaaccccgaa ananaggcnt tacnatacct tngaaaantc 360
tccngccnna aaaagaaaga agctttcnga ttcttaacc 399

<210> 45
<211> 440
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(440)
<223> n = A,T,C or G

<400> 45
gcgggagcag aagctaaagc caaagcccaa gagagtggca gtgccagcac tggtgccagt 60
accagtacca ataacagtgc cagtgccagt gccagcacca gtggtggctt cagtgctggt 120
gccagcctga ccgccactct cacatttggg ctcttcgctg gccttggtgg agctggtgcc 180
agcaccagtg gcagctctgg tgcctgtggt ttctcctaca agtgagattt taggtatctg 240
ccttggtttc agtggggaca tctggggctt anggggcngg gataaggagc tggatgattc 300
taggaaggcc cangttggag aangatgtgn anagtgtgcc aagacactgc ttttggcatt 360
ttattccttt ctgtttgctg gangtcaatt gacccttnna ntttctctta cttgtgtttt 420
canatatngt taatcctgcc 440

<210> 46
<211> 472
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(472)
<223> n = A,T,C or G

<400> 46
gctctgtaat ttcacatttt aaaccttccc ttgacctcac attcctcttc ggccacctct 60
gtttctctgt tcctcttcac agcaaaaact gttcaaaaga gttgttgatt actttcattt 120
ccactttctc accccсattc tcccctcaat taactctcct tcatccccat gatgccatta 180
tgtggctntt attanagtca ccaaccttat tctccaaaac anaagcaaca aggactttga 240
cttctcagca gcactcagct ctggtncttg aaacaccccc gttacttgct attcctccta 300
cctcataaca atctccttcc cagcctctac tgctgccttc tctgagttct tcccagggtc 360
ctaggctcag atgtagtgta gctcaaccct gctacacaaa gnaatctcct gaaagcctgt 420
aaaaatgtcc atncntgtcc tgtgagtgat ctnccangna naataacaaa tt 472

<210> 47
<211> 550
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(550)
<223> n = A,T,C or G

<400> 47
```
ccttcctccg cctggccatc cccagcatgc tcatgctgtg catggagtgg tgggcctatg     60
aggtcgggag cttcctcagt ggtctgtatg aggatggatg acggggactg gtgggaacct    120
gggggccctg tctgggtgca aggcgacagc tgtctttctt caccaggcat cctcggcatg    180
gtggagctgg gcgctcagtc catcgtgtat gaactggcca tcattgtgta catggtccct    240
gcaggcttca gtgtggctgc cagtgtccgg gtangaaacg ctctgggtgc tggagacatg    300
gaagcaggca cggaagtcct ctaccgtttc cctgctgatt acagtgctct ttgctgtanc    360
cttcagtgtc ctgctgttaa gctgtaagga tcacntgggg tacattttta ctaccgaccg    420
agaacatcat taatctggtg gctcaggtgg ttccaattta tgctgtttcc cacctctttg    480
aagctcttgc tgctcaggta cacgccaatt ttgaaaagta aacaacgtgc ctcggagtgg    540
gaattctgct                                                           550
```

<210> 48
<211> 214
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(214)
<223> n = A,T,C or G

<400> 48
```
agaaggacat aaacaagctg aacctgccca agacgtgtga tatcagcttc tcagatccag     60
acaacctcct caacttcaag ctggtcatct gtcctgatna gggcttctac nagagtggga    120
agtttgtgtt cagttttaag gtgggccagg gttacccgca tgatcccccc aaggtgaagt    180
gtgagacnat ggtctatcac cccnacattg acct                                214
```

<210> 49
<211> 267
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(267)
<223> n = A,T,C or G

<400> 49
```
atctgcctaa aatttattca aataatgaaa atnaatctgt tttaagaaat tcagtctttt     60
agtttttagg acaactatgc acaaatgtac gatggagaat tctttttgga tnaactctag    120
gtngaggaac ttaatccaac cggagctntt gtgaaggtca gaanacagga gagggaatct    180
tggcaaggaa tggagacnga gtttgcaaat tgcagctaga gtnaatngtt ntaaatggga    240
ctgctnttgt gtctcccang gaaagtt                                        267
```

<210> 50
<211> 300
<212> DNA
<213> Homo sapien

<220>

<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

<400> 50
gactgggtca aagctgcatg aaaccaggcc ctggcagcaa cctgggaatg gctggaggtg 60
ggagagaacc tgacttctct ttccctctcc ctcctccaac attactggaa ctctgtcctg 120
ttgggatctt ctgagcttgt ttccctgctg ggtgggacag aggacaaagg agaagggagg 180
gtctagaaga ggcagccctt ctttgtcctc tggggtnaat gagcttgacc tanagtagat 240
ggagagacca anagcctctg atttttaatt tccataanat gttcnaagta tatntntacc 300

<210> 51
<211> 300
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(300)
<223> n = A,T,C or G

<400> 51
gggtaaaatc ctgcagcacc cactctggaa aatactgctc ttaattttcc tgaaggtggc 60
cccctatttc tagttggtcc aggattaggg atgtggggta tagggcattt aaatcctctc 120
aagcgctctc caagcacccc cggcctgggg gtnagtttct catcccgcta ctgctgctgg 180
gatcaggttn aataaatgga actcttcctg tctggcctcc aaagcagcct aaaaactgag 240
gggctctgtt agaggggacc tccaccctnn ggaagtccga ggggctnggg aagggtttct 300

<210> 52
<211> 267
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(267)
<223> n = A,T,C or G

<400> 52
aaaatcaact tcntgcatta atanacanat tctanancag gaagtgaana taattttctg 60
cacctatcaa ggaacnnact tgattgcctc tattnaacan atatatcgag ttnctatact 120
tacctgaata ccnccgcata actctcaacc nanatncntc nccatgacac tcnttcttna 180
atgctantcc cgaattcttc attatatcng tgatgttcgn cctgntnata tatcagcaag 240
gtatgtnccn taactgccga nncaang 267

<210> 53
<211> 401
<212> DNA
<213> Homo sapien

<400> 53
agsctttagc atcatgtaga agcaaactgc acctatggct gagataggtg caatgaccta 60
caagattttg tgttttctag ctgtccagga aaagccatct tcagtcttgc tgacagtcaa 120
agagcaagtg aaaccatttc cagcctaaac tacataaaag cagccgaacc aatgattaaa 180
gacctctaag gctccataat catcattaaa tatgcccaaa ctcattgtga ctttttattt 240

tatatacagg attaaaatca acattaaatc atcttattta catggccatc ggtgctgaaa 300
ttgagcattt taaatagtac agtaggctgg tatacattag gaaatggact gcactggagg 360
caaatagaaa actaaagaaa ttagataggc tggaaatgct t 401

<210> 54
<211> 401
<212> DNA
<213> Homo sapien

<400> 54
cccaacacaa tggataaaaa cacttatagt aaatggggac attcactata atgatctaag 60
aagctacaga ttgtcatagt tgttttcctg ctttacaaaa ttgctccaga tctggaatgc 120
cagtttgacc tttgtcttct ataatatttc cttttttcc cctctttgaa tctctgtata 180
tttgattctt aactaaaatt gttctcttaa atattctgaa tcctggtaat taaaagtttg 240
ggtgtatttt ctttacctcc aaggaaagaa ctactagcta caaaaaatat tttggaataa 300
gcattgtttt ggtataaggt acatattttg gttgaagaca ccagactgaa gtaaacagct 360
gtgcatccaa tttattatag ttttgtaagt aacaatatgt a 401

<210> 55
<211> 933
<212> DNA
<213> Homo sapien

<400> 55
tttactgctt ggcaaagtac cctgagcatc agcagagatg ccgagatgaa atcagggaac 60
tcctagggga tgggtcttct attacctggg aacacctgag ccagatgcct tacaccacga 120
tgtgcatcaa ggaatgcctc cgcctctacg caccggtagt aaactatccc ggttactcga 180
caaacccatc acctttccag atggacgctc cttacctgca ggaataactg tgtttatcaa 240
tatttgggct cttcaccaca acccctattt ctgggaagac cctcaggtct ttaacccctt 300
gagattctcc agggaaaatt ctgaaaaaat acatccctat gccttcatac cattctcagc 360
tggattaagg aactgcattg ggcagcattt tgccataatt gagtgtaaag tggcagtggc 420
attaactctg ctccgcttca agctggctcc agaccactca aggccaccca gctgtcgtca 480
agttgcctca agtccaagaa tggaatccat gtgtttgcaa aaaaagtttg ctaattttaa 540
gtccttttcg tataagaatt aakgagacaa ttttcctacc aaaggaagaa caaaaggata 600
aatataatac aaaatatatg tatatggttg tttgacaaat tatataactt aggatacttc 660
tgactggttt tgacatccat taacagtaat tttaatttct ttgctgtatc tggtgaaacc 720
cacaaaaaca cctgaaaaaa ctcaagctga gttccaatgc gaagggaaat gattggtttg 780
ggtaactagt ggtagagtgg ctttcaagca tagtttgatc aaaactccac tcagtatctg 840
cattactttt atctctgcaa atatctgcat gatagcttta ttctcagtta tctttcccca 900
taataaaaaa tatctgccaa aaaaaaaaaa aaa 933

<210> 56
<211> 480
<212> DNA
<213> Homo sapien

<400> 56
ggctttgaag catttttgtc tgtgctccct gatcttcagg tcaccaccat gaagttctta 60
gcagtcctgg tactcttggg agtttccatc tttctggtct ctgcccagaa tccgacaaca 120
gctgctccag ctgacacgta tccagctact ggtcctgctg atgatgaagc ccctgatgct 180
gaaaccactg ctgctgcaac cactgcgacc actgctgctc ctaccactgc aaccaccgct 240
gcttctacca ctgctcgtaa agacattcca gttttaccca aatgggttgg ggatctcccg 300
aatggtagag tgtgtccctg agatggaatc agcttgagtc ttctgcaatt ggtcacaact 360
attcatgctt cctgtgattt catccaacta cttaccttgc ctacgatatc ccctttatct 420
ctaatcagtt tattttcttt caaataaaaa ataactatga gcaacaaaaa aaaaaaaaaa 480

<210> 57
<211> 798
<212> DNA
<213> Homo sapien

<400> 57
agcctacctg gaaagccaac cagtcctcat aatggacaag atccaccagc tcctcctgtg 60
gactaacttt gtgatatggg aagtgaaaat agttaacacc ttgcacgacc aaacgaacga 120
agatgaccag agtactctta accccttaga actgtttttc cttttgtatc tgcaatatgg 180
gatggtattg ttttcatgag cttctagaaa tttcacttgc aagtttattt ttgcttcctg 240
tgttactgcc attcctattt acagtatatt tgagtgaatg attatatttt taaaaagtta 300
catggggctt ttttggttgt cctaaactta caaacattcc actcattctg tttgtaactg 360
tgattataat ttttgtgata atttctggcc tgattgaagg aaatttgaga ggtctgcatt 420
tatatatttt aaatagattt gataggtttt taaattgctt tttttcataa ggtatttata 480
aagttatttg gggttgtctg ggattgtgtg aaagaaaatt agaaccccgc tgtatttaca 540
tttaccttgg tagtttattt gtggatggca gttttctgta gttttgggga ctgtggtagc 600
tcttggattg ttttgcaaat tacagctgaa atctgtgtca tggattaaac tggcttatgt 660
ggctagaata ggaagagaga aaaaatgaaa tggttgttta ctaattttat actcccatta 720
aaaattttta atgttaagaa aaccttaaat aaacatgatt gatcaatatg gaaaaaaaaa 780
aaaaaaaaaa aaaaaaaa 798

<210> 58
<211> 280
<212> DNA
<213> Homo sapien

<400> 58
ggggcagctc ctgaccctcc acagccacct ggtcagccac cagctggggc aacgagggtg 60
gaggtcccac tgagcctctc gcctgccccc gccactcgtc tggtgcttgt tgatccaagt 120
cccctgcctg gtcccccaca aggactccca tccaggcccc ctctgccctg ccccttgtca 180
tggaccatgg tcgtgaggaa gggctcatgc cccttattta tgggaaccat ttcattctaa 240
cagaataaac cgagaaggaa accagaaaaa aaaaaaaaaa 280

<210> 59
<211> 382
<212> DNA
<213> Homo sapien

<400> 59
aggcgggagc agaagctaaa gccaaagccc aagagagtgg cagtgccagc actggtgcca 60
gtaccagtac caataacagt gccagtgcca gtgccagcac cagtggtggc ttcagtgctg 120
gtgccagcct gaccgccact ctcacatttg ggctcttcgc tggccttggt ggagctggtg 180
ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt 240
gttaatcctg ccagtctttc tcttcaagcc agggtgcatc ctcagaaacc tactcaacac 300
agcactctag gcagccacta tcaatcaatt gaagttgaca ctctgcatta aatctatttg 360
ccattaaaaa aaaaaaaaaa aa 382

<210> 60
<211> 602
<212> DNA
<213> Homo sapien

<400> 60
tgaagagccg cgcggtggag ctgctgcccg atgggactgc caaccttgcc aagctgcagc 60

```
ttgtggtgga gaatagtgcc cagcgggtca tccacttggc gggtcagtgg gagaagcacc    120
gggtcccatc ctcgtgagta ccgccactcc gaaagctgca ggattgcaga gagctggaat    180
cttctcgacg gctggcagag atccaagaac tgcaccagag tgtccgggcg gctgctgaag    240
aggcccgcag gaaggaggag gtctataagc agctgatgtc agagctggag actctgccca    300
gagatgtgtc ccggctggcc tacacccagc gcatcctgga gatcgtgggc aacatccgga    360
agcagaagga agagatcacc aagatcttgt ctgatacgaa ggagcttcag aaggaaatca    420
actccctatc tgggaagctg gaccggacgt ttgcggtgac tgatgagctt gtgttcaagg    480
atgccaagaa ggacgatgct gttcggaagg cctataagta tctagctgct ctgcacgaga    540
actgcagcca gctcatccag accatcgagg acacaggcac catcatgcgg gaggttcgag    600
ac                                                                   602

<210> 61
<211> 1368
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(1368)
<223> n = A,T,C or G

<400> 61
ccagtgagcg cgcgtaatac gactcactat agggcgaatt gggtaccggg cccccccctcg    60
agcggccgcc cttttttttt ttttttttatt gatcagaatt caggctttat tattgagcaa    120
tgaaaacagc taaaacttaa ttccaagcat gtgtagttaa agtttgcaaa gtgggatatt    180
gttcacaaaa cacattcaat gtttaaacac tatttatttg aagaacaaaa tatatttaaa    240
attgtttgct tctaaaaagc ccatttccct ccaagtctaa actttgtaat ttgatattaa    300
gcaatgaagt tattttgtac aatctagtta aacaagcaga atagcactag gcagaataaa    360
aaattgcaca gacgtatgca attttccaag atagcattct ttaaattcag ttttcagctt    420
ccaaagattg gttgcccata atagacttaa acatataatg atggctaaaa aaaataagta    480
tacgaaaatg taaaaaagga aatgtaagtc cactctcaat ctcataaaag gtgagagtaa    540
ggatgctaaa gcaaaataaa tgtaggttct ttttttctgt ttccgtttat catgcaatct    600
gcttctttga tatgccttag ggttacccat ttaagttaga ggttgtaatg caatggtggg    660
aatgaaaatt gatcaaatat acacccttgtc atttcatttc aaattgcggg ctggaaactt    720
ccaaaaaaag ggtaggcatg aagaaaaaaa aaatcmaatc agaacctctt caggggtttg    780
kgktctgata tggcagacar gatacaagtc ccaccaggag atggagcaat tcaaaataag    840
ggtaatgggc tgacaaggta ttattgccag catgggacag aatgagcaac aggctgaaaa    900
gtttttggat tatatagcac ctagagtctc tgatgtaggg aatttttgtt agtcaaacat    960
acgctaaact tccaagggaa aatctttcag gtagcctaag cttgcttttc tagagtgatg    1020
agttgcattg ctactgtgat tttttgaaaa caaactgggt ttgtacaagt gagaaagact    1080
agagagaaag atttagtctt gtttagcaga agccatttta tctgcgtgca catggatcaa    1140
tatttctgat cccctatacc ccaggaaggg caaaatccca aagaaatgtg ttagcaaaat    1200
tggctgatgc tatcatattg ctatggacat tgatcttgcc caacacaatg gaattccacc    1260
acactggact agtggatcca ctagttctag agcggccggc caccgcggtg gagctccagc    1320
ttttgttccc tttagtgagg gttaattgcg cgcttggcgt aatcatnn                 1368

<210> 62
<211> 924
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(924)
<223> n = A,T,C or G
```

<400> 62
caaaggnaca ggaacagctt gnaaagtact gncatncctn cctgcaggga ccagcccttt 60
gcctccaaaa gcaataggaa atttaaaaga tttncactga gaaggggncc acgtttnart 120
tntnaatgtn tcargnanar tnccttncaa atgncrnctn cactnactnr gnatttgggt 180
tnccgnrtnc mgnactatnt caggtttgaa aaactggatc tgccacttat cagttatgtg 240
accttaaaga actccgttaa tttctcagag cctcagtttc cttgtctata agttgggagt 300
aatattaata ctatcatttt tccaaggatt gatgtgaaca ttaatgaggt gaaatgacag 360
atgtgtatca tggttcctaa taaacatcca aaatatagta cttactattg tcattattat 420
tacttgtttg aagctaaaga cctcacaata gaatcccatc cagcccacca gacagagytc 480
tgagttttct agtttggaag agctattaaa taacaacktc tagtgtcaat tctatacttg 540
ttatggtcaa gtaactgggc tcagcatttt acattcattg tctctttaag ttctagcaat 600
gtgaagcagg aactatgatt atattgacta cataaatgaa gaaattgagg ctcagataca 660
ttaagtaatt ctcccagggt cacacagcta gaactggcaa agcctgggat tgatccatga 720
tcttccagca ttgaagaatc ataaatgtaa ataactgcaa ggccttttcc tcagaagagc 780
tcctggtgct tgcaccaacc cactagcact tgttctctac aggggaacat ctgtgggcct 840
gggaatcact gcacgtcgca agagatgttg cttctgatga attattgttc ctgtcagtgg 900
tgtgaaggca aaaaaaaaaa aaaa 924

<210> 63
<211> 1079
<212> DNA
<213> Homo sapien

<400> 63
agtcccaaga actcaataat ctcttatgtt ttcttttgaa gacttatttt aaatattaac 60
tatttcggtg cctgaatgga aaaatataaa cattagctca gagacaatgg ggtacctgtt 120
tggaatccag ctggcagcta taagcaccgt tgaaaactct gacaggcttt gtgccctttt 180
tattaaatgg cctcacatcc tgaatgcagg aatgtgttcg tttaaataaa cattaatctt 240
taatgttgaa ttctgaaaac acaaccataa atcatagttg gtttttctgt gacaatgatc 300
tagtacatta tttcctccac agcaaaccta cctttccaga aggtggaaat tgtatttgca 360
acaatcaggg caaaacccac acttgaaaag cattttacaa tattatatct aagttgcaca 420
gaagacccca gtgatcacta ggaaatctac cacagtccag tttttctaat ccaagaaggt 480
caaacttcgg ggaataatgt gtccctcttc tgctgctgct ctgaaaaata ttcgatcaaa 540
acgaagttta caagcagcag ttattccaag attagagttc atttgtgtat cccatgtata 600
ctggcaatgt ttaggtttgc ccaaaaactc ccagacatcc acaatgttgt tgggtaaacc 660
accacatctg gtaacctctc gatcccttag atttgtatct cctgcaaata taactgtagc 720
tgactctgga gcctcttgca ttttctttaa aaccattttt aactgattca ttcgttccgc 780
agcatgccct ctggtgctct ccaaatggga tgtcataagg caaagctcat ttcctgacac 840
attcacatgc acacataaaa ggtttctcat cattttggta cttggaaaag gaataatctc 900
ttggcttttt aatttcactc ttgatttctt caacattata gctgtgaaat atccttcttc 960
atgacctgta ataatctcat aattacttga tctcttcttt aggtagctat aatatggggg 1020
aataacttcc tgtagaaata tcacatctgg gctgtacaaa gctaagtagg aacacaccc 1079

<210> 64
<211> 1001
<212> DNA
<213> Homo sapien

<400> 64
gaatgtgcaa cgatcaagtc agggtatctg tggtatccac cactttgagc atttatcgat 60
tctatatgtc aggaacattt caagttatct gttctagcaa ggaaatataa aatacttata 120
gttaactatg gcctatctac agtgcaacta aaaactagat tttattcctt tccacctgtg 180
ggtttgtatt catttaccac cctcttttca ttccctttct cacccacaca ctgtgccggg 240
cctcaggcat atactattct actgtctgtc tctgtaagga ttatcatttt agcttccaca 300

tatgagagaa tgcatgcaaa gtttttcttt ccatgtctgg cttatttcac ttaacataat 360
gacctccgct tccatccatg ttatttatat tacccaatag tgttcataaa tatatataca 420
cacatatata ccacattgca tttgtccaat tattcattga cggaaactgg ttaatgttat 480
atcgttgcta ttgtggatag tgctgcaata aacacgcaag tggggatata atttgaagag 540
ttttttgtt gatgttcctc caaattttaa gattgttttg tctatgtttg tgaaaatggc 600
gttagtattt tcatagagat tgcattgaat ctgtagattg ctttgggtaa gtatggttat 660
tttgatggta ttaatttttt cattccatga agatgagatg tctttccatt gtttgtgtcc 720
tctacatttt ctttcatcaa agttttgttg tatttttgaa gtagatgtat ttcaccttat 780
agatcaagtg tattccctaa atattttatt tttgtagcta ttgtagatga aattgccttc 840
ttgatttctt tttcacttaa ttcattatta gtgtatggaa atgttatgga tttttatttg 900
ttggttttta atcaaaaact gtattaaact tagagttttt tgtggagttt ttaagttttt 960
ctagatataa gatcatgaca tctaccaaaa aaaaaaaaaa a 1001

<210> 65
<211> 575
<212> DNA
<213> Homo sapien

<400> 65
acttgatata aaaaggatat ccataatgaa tattttatac tgcatccttt acattagcca 60
ctaaatacgt tattgcttga tgaagacctt tcacagaatc ctatggattg cagcatttca 120
cttggctact tcatacccat gccttaaaga ggggcagttt ctcaaaagca gaaacatgcc 180
gccagttctc aagttttcct cctaactcca tttgaatgta agggcagctg gcccccaatg 240
tggggaggtc cgaacatttt ctgaattccc atttcttgt tcgcggctaa atgacagttt 300
ctgtcattac ttagattccc gatctttccc aaaggtgttg atttacaaag aggccagcta 360
atagccagaa atcatgaccc tgaaagagag atgaaatttc aagctgtgag ccaggcagga 420
gctccagtat ggcaaaggtt cttgagaatc agccatttgg tacaaaaaag atttttaaag 480
cttttatgtt ataccatgga gccatagaaa ggctatggat tgtttaagaa ctattttaaa 540
gtgttccaga cccaaaaagg aaaaaaaaaa aaaaa 575

<210> 66
<211> 831
<212> DNA
<213> Homo sapien

<400> 66
attgggctcc ttctgctaaa cagccacatt gaaatggttt aaaagcaagt cagatcaggt 60
gatttgtaaa attgtattta tctgtacatg tatgggcttt taattcccac caagaaagag 120
agaaattatc tttttagtta aaaccaaatt tcacttttca aaatatcttc caacttattt 180
attggttgtc actcaattgc ctatatatat atatatatat gtgtgtgtgt gtgtgtgcgc 240
gtgagcgcac gtgtgtgtat gcgtgcgcat gtgtgtgtat gtgtattatc agacataggt 300
ttctaacttt tagatagaag aggagcaaca tctatgccaa atactgtgca ttctacaatg 360
gtgctaatct cagacctaaa tgatactcca tttaatttaa aaaagagttt taaataatta 420
tctatgtgcc tgtatttccc ttttgagtgc tgcacaacat gttaacatat tagtgtaaaa 480
gcagatgaaa caaccacgtg ttctaaagtc tagggattgt gctataatcc ctatttagtt 540
caaaattaac cagaattctt ccatgtgaaa tggaccaaac tcatattatt gttatgtaaa 600
tacagagttt taatgcagta tgacatccca caggggaaaa gaatgtctgt agtgggtgac 660
tgttatcaaa tattttatag aatacaatga acggtgaaca gactggtaac ttgtttgagt 720
tcccatgaca gatttgagac ttgtcaatag caaatcattt ttgtatttaa atttttgtac 780
tgatttgaaa aacatcatta aatatcttta aaagtaaaaa aaaaaaaaaa a 831

<210> 67
<211> 590
<212> DNA
<213> Homo sapien

<400> 67
gtgctctgtg tattttttta ctgcattaga cattgaatag taatttgcgt taagatacgc 60
ttaaaggctc tttgtgacca tgtttccctt tgtagcaata aaatgttttt tacgaaaact 120
ttctccctgg attagcagtt taaatgaaac agagttcatc aatgaaatga gtatttaaaa 180
taaaaatttg ccttaatgta tcagttcagc tcacaagtat tttaagatga ttgagaagac 240
ttgaattaaa gaaaaaaaaa ttctcaatca tatttttaaa atataagact aaaattgttt 300
ttaaaacaca tttcaaatag aagtgagttt gaactgacct tatttatact ctttttaagt 360
ttgttccttt tccctgtgcc tgtgtcaaat cttcaagtct tgctgaaaat acatttgata 420
caaagttttc tgtagttgtg ttagttcttt tgtcatgtct gtttttggct gaagaaccaa 480
gaagcagact tttcttttaa aagaattatt tctctttcaa atatttctat ccttttttaa 540
aaattccttt ttatggctta tatacctaca tatttaaaaa aaaaaaaaaa 590

<210> 68
<211> 291
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(291)
<223> n = A,T,C or G

<400> 68
gttccctttt ccggtcggcg tggtcttgcg agtggagtgt ccgctgtgcc cgggcctgca 60
ccatgagcgt cccggccttc atcgacatca gtgaagaaga tcaggctgct gagcttcgtg 120
cttatctgaa atctaaagga gctgagattt cagaagagaa ctcggaaggt ggacttcatg 180
ttgatttagc tcaaattatt gaagcctgtg atgtgtgtct gaaggaggat gataaagatg 240
ttgaaagtgt gatgaacagt ggggnatcct actcttgatc cggaanccna c 291

<210> 69
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 69
tctatgagca tgccaaggct ctgtgggagg atgaaggagt gcgtgcctgc tacgaacgct 60
ccaacgagta ccagctgatt gactgtgccc agtacttcct ggacaagatc gacgtgatca 120
agcaggctga ctatgtgccg agcgatcagg acctgcttcg ctgccgtgtc ctgacttctg 180
gaatctttga gaccaagttc caggtggacn aagtcaactt ccacatgntt gacgtgggtg 240
gccagcgcga tgaacgccgc aagtggatcc agtgcttcaa cgatgtgact gccatcatct 300
t 301

<210> 70
<211> 201
<212> DNA
<213> Homo sapien

<400> 70
gcggctcttc ctcgggcagc ggaagcggcg cggcggtcgg agaagtggcc taaaacttcg 60

gcgttgggtg aaagaaaatg gcccgaacca agcagactgc tcgtaagtcc accggtggga 120
aagccccccg caaacagctg gccacgaaag ccgccaggaa aagcgctccc tctaccggcg 180
gggtgaagaa gcctcatcgc t 201

<210> 71
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 71
gccggggtag tcgccgncgc cgccgccgct gcagccactg caggcaccgc tgccgccgcc 60
tgagtagtgg gcttaggaag gaagaggtca tctcgctcgg agcttcgctc ggaagggtct 120
ttgttccctg cagccctccc acgggaatga caatggataa aagtgagctg gtacanaaag 180
ccaaactcgc tgagcaggct gagcgatatg atgatatggc tgcagccatg aaggcagtca 240
cagaacaggg gcatgaactc ttcaacgaag agagaaatct gctctctggt gcctacaaga 300
a 301

<210> 72
<211> 251
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(251)
<223> n = A,T,C or G

<400> 72
cttggggggt gttgggggag agactgtggg cctggaaata aaacttgtct cctctaccac 60
caccctgtac cctagcctgc acctgtccac atctctgcaa agttcagctt ccttccccag 120
gtctctgtgc actctgtctt ggatgctctg gggagctcat gggtggagga gtctccacca 180
gagggaggct caggggactg gttgggccag ggatgaatat ttgagggata aaaattgtgt 240
aagagccaan g 251

<210> 73
<211> 895
<212> DNA
<213> Homo sapien

<400> 73
tttttttttt tttttcccag gccctctttt tatttacagt gataccaaac catccacttg 60
caaattcttt ggtctcccat cagctggaat taagtaggta ctgtgtatct ttgagatcat 120
gtatttgtct ccactttggt ggatacaaga aaggaaggca cgaacagctg aaaaagaagg 180
gtatcacacc gctccagctg gaatccagca ggaacctctg agcatgccac agctgaacac 240
ttaaaagagg aaagaaggac agctgctctt catttatttt gaaagcaaat tcatttgaaa 300
gtgcataaat ggtcatcata agtcaaacgt atcaattaga ccttcaacct aggaaacaaa 360
attttttttt tctatttaat aatacaccac actgaaatta tttgccaatg aatcccaaag 420
atttggtaca aatagtacaa ttcgtatttg ctttcctctt tcctttcttc agacaaacac 480
caaataaaat gcaggtgaaa gagatgaacc acgactagag gctgacttag aaatttatgc 540
tgactcgatc taaaaaaaat tatgttggtt aatgttaatc tatctaaaat agagcatttt 600

gggaatgctt ttcaaagaag gtcaagtaac agtcatacag ctagaaaagt ccctgaaaaa 660
aagaattgtt aagaagtata ataacctttt caaaacccac aatgcagctt agttttcctt 720
tatttatttg tggtcatgaa gactatcccc atttctccat aaaatcctcc ctccatactg 780
ctgcattatg gcacaaaaga ctctaagtgc caccagacag aaggaccaga gtttctgatt 840
ataaacaatg atgctgggta atgtttaaat gagaacattg gatatggatg gtcag 895

<210> 74
<211> 351
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(351)
<223> n = A,T,C or G

<400> 74
tgtgcncagg ggatgggtgg gcngtggaga ngatgacaga aaggctggaa ggaangggggg 60
tgggtttgaa ggccanggcc aaggggncct caggtccgnt tctgnnaagg gacagccttg 120
aggaaggagn catggcaagc catagctagg ccaccaatca gattaagaaa nnctgagaaa 180
nctagctgac catcactgtt ggtgnccagt ttcccaacac aatggaatnc caccacactg 240
gactagngga nccactagtt ctagagcggc cgccaccgcg gtggaacccc aacttttgcc 300
cctttagnga gggttaattg cgcgcttggc ntaatcatgg tcataagctg t 351

<210> 75
<211> 251
<212> DNA
<213> Homo sapien

<400> 75
tacttgacct tctttgaaaa gcattcccaa aatgctctat tttagataga ttaacattaa 60
ccaacataat ttttttttaga tcgagtcagc ataaatttct aagtcagcct ctagtcgtgg 120
ttcatctctt tcacctgcat tttatttggt gtttgtctga agaaaggaaa gaggaaagca 180
aatacgaatt gtactatttg taccaaatct ttgggattca ttggcaaata atttcagtgt 240
ggtgtattat t 251

<210> 76
<211> 251
<212> DNA
<213> Homo sapien

<400> 76
tatttaataa tacaccacac tgaaattatt tgccaatgaa tcccaaagat ttggtacaaa 60
tagtacaatt cgtatttgct ttcctctttc ctttcttcag acaaacacca aataaaatgc 120
aggtgaaaga gatgaaccac gactagaggc tgacttagaa atttatgctg actcgatcta 180
aaaaaaatta tgttggttaa tgttaatcta tctaaaatag agcattttgg gaatgctttt 240
caaagaaggt c 251

<210> 77
<211> 351
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature

<222> (1)...(351)
<223> n = A,T,C or G

<400> 77
actcaccgtg ctgtgtgctg tgtgcctgct gcctggcagc ctggccctgc cgctgctcag 60
gaggcgggag gcatgagtga gctacagtgg gaacaggctc aggactatct caagagannn 120
tatctctatg actcagaaac aaaaaatgcc aacagtttag aagccaaact caaggagatg 180
caaaaattct ttggcctacc tataactgga atgttaaact cccgcgtcat agaaataatg 240
cagaagccca gatgtggagt gccagatgtt gcagaatact cactatttcc aaatagccca 300
aaatggactt ccaaagtggt cacctacagg atcgtatcat atactcgaga c 351

<210> 78
<211> 1574
<212> DNA
<213> Homo sapien

<400> 78
gccctggggg cggaggggag gggcccacca cggccttatt tccgcgagcg ccggcactgc 60
ccgctccgag cccgtgtctg tcgggtgccg agccaacttt cctgcgtcca tgcagccccg 120
ccggcaacgg ctgcccgctc cctggtccgg gcccaggggc ccgcgcccca ccgccccgct 180
gctcgcgctg ctgctgttgc tcgccccggt ggcggcgccc gcggggtccg gggaccccga 240
cgaccctggg cagcctcagg atgctggggt cccgcgcagg ctcctgcagc aggcggcgcg 300
cgcggcgctt cacttcttca acttccggtc cggctcgccc agcgcgctgc gagtgctggc 360
cgaggtgcag gagggccgcg cgtggattaa tccaaaagag ggatgtaaag ttcacgtggt 420
cttcagcaca gagcgctaca acccagagtc tttacttcag gaaggtgagg gacgtttggg 480
gaaatgttct gctcgagtgt ttttcaagaa tcagaaaccc agaccaacta tcaatgtaac 540
ttgtacacgg ctcatcgaga aaaagaaaag acaacaagag gattacctgc tttacaagca 600
aatgaagcaa ctgaaaaacc ccttggaaat agtcagcata cctgataatc atggacatat 660
tgatccctct ctgagactca tctgggattt ggctttcctt ggaagctctt acgtgatgtg 720
ggaaatgaca acacaggtgt cacactacta cttggcacag ctcactagtg tgaggcagtg 780
gaaaactaat gatgatacaa ttgattttga ttatactgtt ctacttcatg aattatcaac 840
acaggaaata attccctgtc gcattcactt ggtctggtac cctggcaaac ctcttaaagt 900
gaagtaccac tgtcaagagc tacagacacc agaagaagcc tccggaactg aagaaggatc 960
agctgtagta ccaacagagc ttagtaattt ctaaaaagaa aaaatgatct tttccgact 1020
tctaaacaag tgactatact agcataaatc attcttctag taaaacagct aaggtataga 1080
cattctaata atttgggaaa acctatgatt acaagtaaaa actcagaaat gcaaagatgt 1140
tggtttttg tttctcagtc tgctttagct tttaactctg gaagcgcatg cacactgaac 1200
tctgctcagt gctaaacagt caccagcagg ttcctcaggg tttcagccct aaaatgtaaa 1260
acctggataa tcagtgtatg ttgcaccaga atcagcattt ttttttaac tgcaaaaaat 1320
gatggtctca tctctgaatt tatatttctc attcttttga acatactata gctaatatat 1380
tttatgttgc taaattgctt ctatctagca tgttaaacaa agataatata ctttcgatga 1440
aagtaaatta taggaaaaaa attaactgtt ttaaaaagaa cttgattatg ttttatgatt 1500
tcaggcaagt attcattttt aacttgctac ctacttttaa ataaatgttt acatttctaa 1560
aaaaaaaaaa aaaa 1574

<210> 79
<211> 401
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(401)
<223> n = A,T,C or G

<400> 79
catactgtga attgttcttg actccttttc ttgacattca gttttcanaa tttccatctt 60
tcttctggaa ctaatgtgct gttctcttga ctgcctgctg ggccagcatc cgattgccag 120
ccagaaacgt cacactgccc aagatggcca ggtacttcaa ggtctggaac atgttgagct 180
gagtccagta gacatacatg agtcccagca tagcagcatg tcccaggtga aatataatcg 240
tgctaggagc aaaagtgaag ttggagacat tggcaccaat ccggatccac tagttctaga 300
gcggccgcca ccgcggtgga gctccagctt ttgttccctt tagtgagggt taattgcgcg 360
cttggcgtaa tcatggncat agctgtttcc tgtgtgaaat t 401

<210> 80
<211> 301
<212> DNA
<213> Homo sapien

<400> 80
aaaaatgaaa catctatttt agcagcaaga ggctgtgagg gatggggtag aaaaggcatc 60
ctgagagagt tctagaccga cccaggtcct gtggcacact atacgggtca ggaggggtgg 120
aagacaggcc taagctctag gacggtgaat ctcggggcta tttgtggatt tgttagaaac 180
agacattctt ttggcctttt cctggcactg gtgttgccgg caggtgggca gaagtgagcc 240
accagtcact gttcagtcat tgccaccaca gatcttcagc agaatcttcc ggtaatcccc 300
t 301

<210> 81
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 81
tagccaggtt gctcaagcta attttattct ttcccaacag gatccatttg gaaaatatca 60
agcctttaga atgtggcagc aagagaaagc ggactacgca ggaacgggga gtttgggaga 120
agctctcctg gtgttgactt agggatgaag gctccaggct gctgccagaa atggagtcac 180
cagcagaaga actgntttct ctgataagga tgtcccacca ttttcaagct gttcgttaaa 240
gttacacagg tccttcttgc agcagtaagt accgttagct cattttccct caagcgggtt 300
t 301

<210> 82
<211> 201
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(201)
<223> n = A,T,C or G

<400> 82
tcaacagaca aaaaaagttt attgaataca aaactcaaag gcatcaacag tcctgggccc 60
aagagatcca tggcaggaag tcaagagttc tgcttcaggg tcggtctggg cagccctgga 120
agaagtcatt gcacatgaca gtgatgagtg ccaggaaaac agcatactcc tggaaagtcc 180
acctgctggn cactgnttca t 201

<210> 83
<211> 251
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(251)
<223> n = A,T,C or G

<400> 83
gtaaggagca tactgtgccc atttattata gaatgcagtt aaaaaaaata ttttgaggtt 60
agcctctcca gtttaaaagc acttaacaag aaacacttgg acagcgatgc aatggtctct 120
cccaaaccgg ctccctctta ccaagtaccg taaacagggt ttgagaacgt tcaatcaatt 180
tcttgatatg aacaatcaaa gcatttaatg caaacatatt tgcttctcaa anaataaaac 240
cattttccaa a 251

<210> 84
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 84
agtttataat gttttactat gatttagggc tttttttca aagaacaaaa attataagca 60
taaaaactca ggtatcagaa agactcaaaa ggctgttttt cactttgttc agattttgtt 120
tccaggcatt aagtgtgtca tacagttgtt gccactgctg ttttccaaat gtccgatgtg 180
tgctatgact gacaactact tttctctggg tctgatcaat tttgcagtan accattttag 240
ttcttacggc gtcnataaca aatgcttcaa catcatcagc tccaatctga agtcttgctg 300
c 301

<210> 85
<211> 201
<212> DNA
<213> Homo sapien

<400> 85
tatttgtgta tgtaacattt attgacatct acccactgca agtatagatg aataagacac 60
agtcacacca taaaggagtt tatccttaaa aggagtgaaa gacattcaaa aaccaactgc 120
aataaaaaag ggtgacataa ttgctaaatg gagtggagga acagtgctta tcaattcttg 180
attgggccac aatgatatac c 201

<210> 86
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)

<223> n = A,T,C or G

<400> 86
tttataaaat attttattta cagtagagct ttacaaaaat agtcttaaat taatacaaat 60
cccttttgca atataactta tatgactatc ttctcaaaaa cgtgacattc gattataaca 120
cataaactac atttatagtt gttaagtcac cttgtagtat aaatatgttt tcatcttttt 180
tttgtaataa ggtacatacc aataacaatg aacaatggac aacaaatctt attttgntat 240
tcttccaatg taaaattcat ctctggccaa aacaaaatta accaaagaaa agtaaaacaa 300
t 301

<210> 87
<211> 351
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(351)
<223> n = A,T,C or G

<400> 87
aaaaaagatt taagatcata aataggtcat tgttgtcaca acacatttca gaatcttaaa 60
aaaacaaaca ttttggcttt ctaagaaaaa gacttttaaa aaaaatcaat tccctcatca 120
ctgaaaggac ttgtacattt ttaaacttcc agtctcctaa ggcacagtat ttaatcagaa 180
tgccaatatt accaccctgc tgtagcanga ataaagaagc aagggattaa cacttaaaaa 240
aacngccaaa ttcctgaacc aaatcattgg cattttaaaa aagggataaa aaaacnggnt 300
aagggggga gcattttaag taaagaangg ccaagggtgg tatgccngga c 351

<210> 88
<211> 301
<212> DNA
<213> Homo sapien

<220>
<221> misc_feature
<222> (1)...(301)
<223> n = A,T,C or G

<400> 88
gttttaggtc tttaccaatt tgattggttt atcaacaggg catgaggttt aaatatatct 60
ttgaggaaag gtaaagtcaa atttgacttc ataggtcatc ggcgtcctca ctcctgtgca 120
ttttctggtg gaagcacaca gttaattaac tcaagtgtgg cgntagcgat gctttttcat 180
ggngtcattt atccacttgg tgaacttgca cacttgaatg naaactcctg ggtcattggg 240
ntggccgcaa gggaaaggtc cccaagacac caaaccttgc agggtacctn tgcacaccaa 300
c 301

<210> 89
<211> 591
<212> DNA
<213> Homo sapien

<400> 89
tttttttttt tttttttatt aatcaaatga ttcaaaacaa ccatcattct gtcaatgccc 60
aagcacccag ctggtcctct ccccacatgt cacactctcc tcagcctctc cccaaccct 120
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<212> DNA
<213> Homo sapien

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<213> Homo sapien

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<213> Homo sapien

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<211> 90
<212> PRT
<213> Homo sapien

<400> 98

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Ala Thr Gly Pro Ala Asp Asp Glu Ala Pro Asp Ala Glu Thr Thr Ala
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Ala Ala Thr Thr Ala Thr Thr Ala Ala Pro Thr Thr Ala Thr Thr Ala
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<213> Homo sapien

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Glu Lys Leu Trp Thr Glu Val Asn Ala Leu Lys Glu Ile Gln Ala Leu
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Gln Thr Val Cys Leu Arg Gly Thr Lys Val His Lys Lys Cys Tyr Leu
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Ala Ser Glu Gly Leu Lys His Phe His Glu Ala Asn Glu Asp Cys Ile
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Ser Lys Gly Gly Ile Leu Val Ile Pro Arg Asn Ser Asp Glu Ile Asn
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Ala Leu Gln Asp Tyr Gly Lys Arg Ser Leu Pro Gly Val Asn Asp Phe
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      <211> 553
      <212> PRT
      <213> Homo sapien

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Ala Ala Gly Ile Thr Tyr Val Pro Pro Leu Leu Leu Glu Val Gly Val
        35                  40                  45
Glu Glu Lys Phe Met Thr Met Val Leu Gly Ile Gly Pro Val Leu Gly
    50                  55                  60
Leu Val Cys Val Pro Leu Leu Gly Ser Ala Ser Asp His Trp Arg Gly
65                  70                  75                  80
Arg Tyr Gly Arg Arg Arg Pro Phe Ile Trp Ala Leu Ser Leu Gly Ile
                85                  90                  95
Leu Leu Ser Leu Phe Leu Ile Pro Arg Ala Gly Trp Leu Ala Gly Leu
            100                 105                 110
Leu Cys Pro Asp Pro Arg Pro Leu Glu Leu Ala Leu Leu Ile Leu Gly
        115                 120                 125
Val Gly Leu Leu Asp Phe Cys Gly Gln Val Cys Phe Thr Pro Leu Glu
    130                 135                 140
Ala Leu Leu Ser Asp Leu Phe Arg Asp Pro Asp His Cys Arg Gln Ala
145                 150                 155                 160
Tyr Ser Val Tyr Ala Phe Met Ile Ser Leu Gly Gly Cys Leu Gly Tyr
                165                 170                 175
Leu Leu Pro Ala Ile Asp Trp Asp Thr Ser Ala Leu Ala Pro Tyr Leu
            180                 185                 190
Gly Thr Gln Glu Glu Cys Leu Phe Gly Leu Leu Thr Leu Ile Phe Leu
        195                 200                 205
Thr Cys Val Ala Ala Thr Leu Leu Val Ala Glu Glu Ala Ala Leu Gly
    210                 215                 220
Pro Thr Glu Pro Ala Glu Gly Leu Ser Ala Pro Ser Leu Ser Pro His
225                 230                 235                 240
Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly Ala Leu
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Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg
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Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe
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Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val
    290                 295                 300
Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly
305                 310                 315                 320
Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu
                325                 330                 335
Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg
            340                 345                 350
Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala
        355                 360                 365
Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu
    370                 375                 380
Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala
385                 390                 395                 400
Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly
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Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu
            420                 425                 430
Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala
        435                 440                 445
Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser
    450                 455                 460
Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala
465                 470                 475                 480
Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp
                485                 490                 495
Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser
            500                 505                 510
Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala
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Lys Ser Asp Leu Ala Lys Tyr Ser Ala
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<212> DNA
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<210> 104
<211> 469
<212> DNA
<213> Human

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<210> 107
<211> 1009
<212> DNA
<213> Human

<400> 107
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